# The American Journal of DIGESTIVE DISEASES

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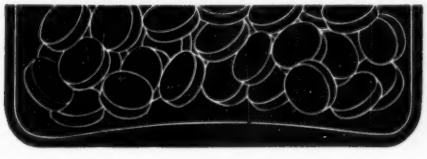

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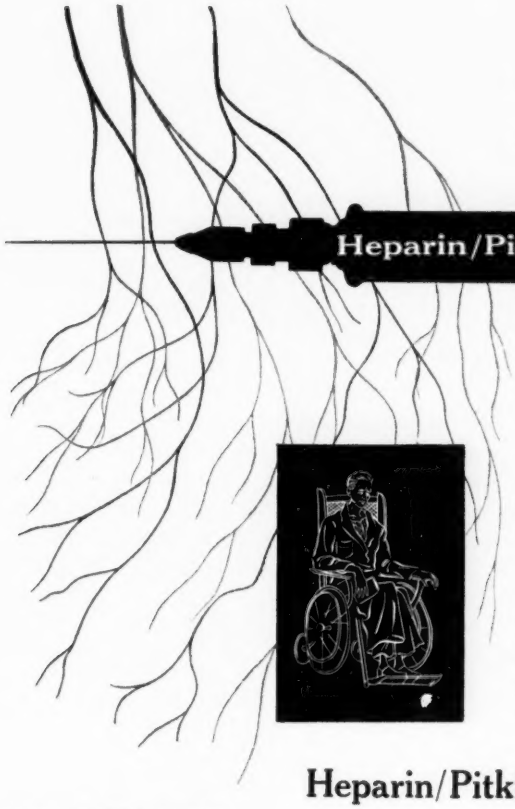


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(2) Evans, J. A., and Dee, J. F.: Anticoagulant Treatment of Postoperative Venous Thrombosis and Pulmonary Embolism, *New Eng. J. M.*, *238*:1, 1948.

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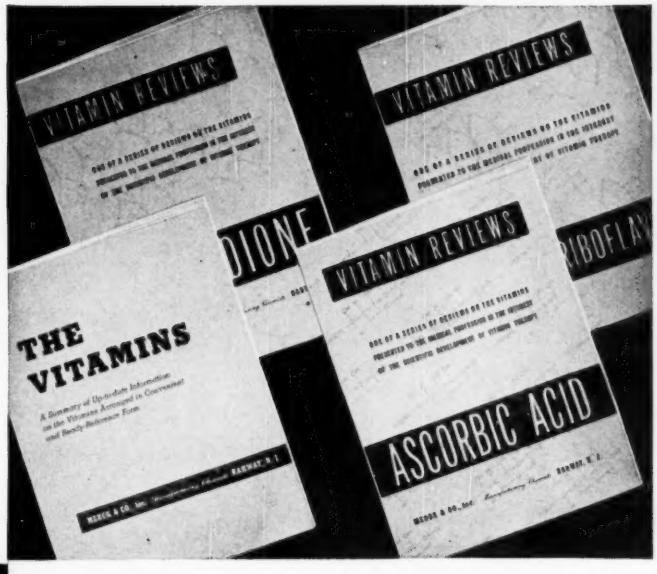
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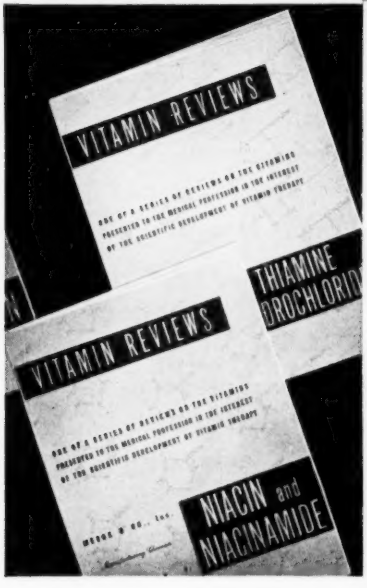


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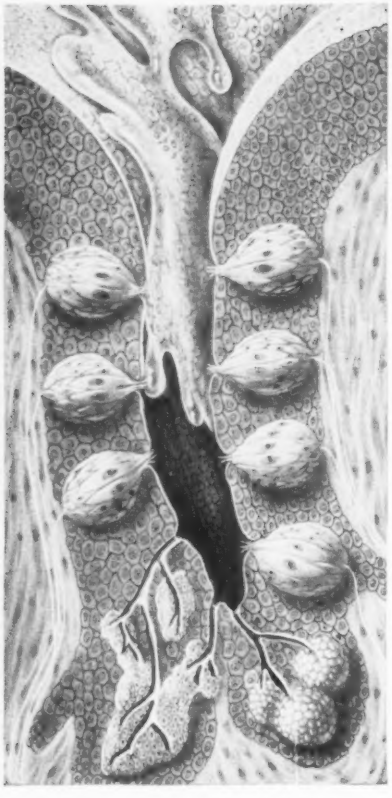

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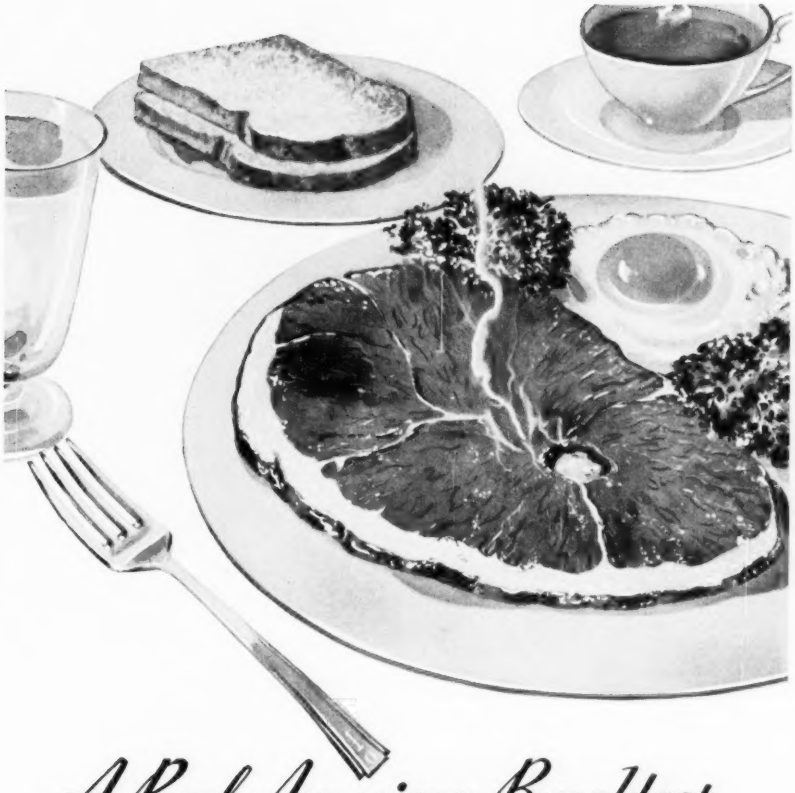

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(1) Thorn, G.W.; Quibby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
(2) Orent-Keiles, E., and Halliman, L.F., Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

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# LIVER FUNCTION TESTS AND HEPARIN

N. C. Jefferson, M. D. and H. Necheles, M. D., Ph.D., F. A. C. P. Chicago, Ill.

CERTAIN dyes are known to form colloidal complexes with fractions of the plasma proteins. Thus, Gregersen and Rawson (1) have shown that a number of relatively simple dyes, paticularly T-1824, Evan's Blue, are firmly bound to plasma albumin. It has been reported that, with the intravenous Congo red test in man, the clearance of the dye was blocked following administration of herapin (2). Larger particles, like colloidal iron oxide or India ink, when introduced into the circulation, seem to acquire a fibrin coating, and are stored rapidly in the cells of the reticuloendothelial system. This storage was prevented by administration of anticoagulants (3). India ink and colloidal iron oxide were found to produce a prolonged delay in the excretion of bromsulfalein (2).

Heparin is a unique substance, having a high molecular weight and a strong negative electric charge, apparently the strongest of any of the organic compounds in the body. It interferes with the Wassermann reaction by neutralizing the serum complement, and it prevents the action of several enzymes (4).

The observations quoted above suggested the possibility that heparinization may affect liver function tests with dyes. The effects of another anticoagulant, dicumarin, on liver function have been investigated by Richards and Cortell, who concluded that "further studies—appear indicated" (5). In this laboratory studies of liver function following doses of dicumarin which prolonged clotting time considerably, indicated diminished liver function with the bromsulfalein test. However, most of the dogs employed in that study had subcutaneous and intramuscular hemorrhages, and their livers showed fatty infiltration. Richards and Sortell (5) and Richards and Steggarda (6) had similar experiences. In addition they found however that, while in normal animals without hemorrhage liver function did not seem to be impaired during dicumarinization, in the case of existing liver damage, dicumarinization produced additional depression of liver function.

Because liver function tests are necessary at times in heparinized patients, and in view of the interesting fundamental considerations mentioned above, a series of dye excretion tests with and without heparin were performed on dogs.

## Methods

Bilirubin and bromsulfalein function tests were performed on apparently normal unanesthetized or anesthetized mongrel dogs. Intravenous sodium pentobarbital, 25 mg. p.kg. was used, because it has been shown to have little or no effect on the liver (7). On each dog one or more dye control tests and one or more dye tests with heparin and, on some dogs, an additional final dye test was performed. The tests were done at intervals of 6 to 14 days. 2 cc of heparin were given intravenously 10 or 30 minutes before injecting the dye. In a number of tests, additional doses of 2 cc of heparin were injected at intervals of 30 minutes. Blood samples were taken usually 15, 30, 60, and 120 minutes, after the injection of bromsulfalein or bilirubin. Dye determinations in the plasma were done with an Evelyn photoelectric colorimeter. Clotting times were estimated with the Lee White method, and were found to be prolonged 2 to 3 fold during the experimental period.

It was observed that the untreated plasma of dogs that had received an intravenous injection of bromsulfalein often showed a pink color, suggesting hemolysis. The degree of this coloration increased with the amounts of bromsulfalein adminstered intravenously, or added to blood in vitro. Tests for hemoglobin (acid-hematin and benzidine) did not bear out that the pink color of the plasma was due to hemolysis. The color of the plasma was found to be due to conversion of some of the leukobase of the bromsulfalein into the dye in the untreated plasma. Apparently, a decrease in the $CO_2$ content of the plasma played a role. Similarly, exposed veins, into which constant injections of bromsulfalein solutions were given, and the tissues surrounding them, acquired a purplish blue color during the experiment.

## Results and Discussion

27 experiments were done on 8 unanesthetized dogs. Seven of these animals were heparinized with 2 cc of heparin and one animal with 8 cc of heparin, given intravenously. Thirty minutes later, four of the dogs received an i. v. injection of 50 mg of bilirubin each, and the other four received an i. v. injection of 75 mg of bromsulfalein each. With bromsulfalein and heparin, the rate of dye clearance was found prolonged in 3 tests and shortened in 3 tests. With bilirubin, the rate of dye clearance was prolonged in 3 tests and shortened in 4 tests. It was felt that the inconsistency of these results was due to the difficulty of complete injection of the dyes into the veins of unanesthetized dogs, and possibly to changes in position of the dogs, incidental to the handling during the withdrawal of blood. The effect on circulation time and on blood flow through the liver, and consequently on dye clearance by changes in body position has been shown by Culbertson et al. (9). Therefore, another series of tests was performed under pentobarbital sodium anesthesia. 28 experiments were done on 10 dogs, using 50 mg each of bilirubin or of bromsulfalein, and 2 to 6 cc of heparin, given 10 minutes before injection of each dye; 8 experiments were performed on 4 dogs using 100 mg. each of bilirubin or of bromsulfalein and 2 to 6 cc of heparin. Analysis of the results showed a delay in bromsulfalein clearance after heparin.

A further series of 18 experiments on 9 different dogs, using 100 mg of bromsulfalein and 4 cc of heparin, yielded inconclusive results.

Statistical analysis of all data obtained revealed, that the clearance of bromsulfalein and of bilirubin is

Aided by a grant from the A. B. Kuppenheimer Fund.

The Department is in part supported by the Michael Reese Research Foundation.

From the Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital and from the Department of Surgery of Provident Hospital, Chicago, Ill.

not affected by heparinization. We are indebted to Dr. H. Silverstone of the Department of Cancer Research for statistical analysis.

Since it has been reported that previous feeding of fat affects the thymol turbidity test (8), similar experiments were carried out with the dye clearance tests. Feeding of meat or of meat and fat was found not to affect the clearance of 100 mg of bromsulfalein in the unanesthetized dog, confirming the results of Ingelfinger (11).

Repeated control dye clearance tests on the same animal showed that dye clearance in the so-called normal dog varied considerably. For example, in repeated clearance tests the 15 minute dye concentrations in the serum of dog No. 56, 14.6 kg. (50 mg bilirubin, unanesthetized) were 6.33, 1.74, and 1.91 respectively; in dog No. 44, 12.8 kg. (50 mg bilirubin, anesthetized) the values were 4.66 and 2.33 respectively. For bromsulfalein in dog No. 38, 11.8 kg. (50 mg bromsulfalein, anesthetized), the values were 0.16 and trace.

In the series of tests which showed statistically significant differences between dye tests without heparin and dye tests with heparin, critical examination of the data makes us feel, that the differences observed were due rather to the great variability of dye clearance by the dog's liver and possibly also to variability in extrahepatic disappearance of dye (10). This is exemplified in the following tests.

Dog No. 44, 12.8 kg. anesthetized, heparin i. v. 10 minutes before i. v. injection of 50 mg bilirubin.

| | MINUTES | 0 | 15 | 30 | 60 | 90 |
|---|---|---|---|---|---|---|
| 2:19 | dye | 0 | 2.33 | 0.83 | 0.24 | 0 |
| 2:26 | dye, 2 cc heparin | 0 | 4.16 | 2.00 | 1.00 | 0.41 |
| 3:5 | dye, 6 cc heparin | 0 | 5.83 | 4.00 | 2.74 | 1.91 |
| 3:12 | dye | 0 | 4.66 | 2.16 | 1.16 | 0.83 |

Dog No. 38, 11.8 kg. unanesthetized, heparin i. v. 10 minutes before i. v. injection of 50 mg bromsulfalein.

| | MINUTES | 0 | 15 | 30 | 60 | 90 |
|---|---|---|---|---|---|---|
| 2:24 | dye | 0 | 0.16 | trace | 0 | 0 |
| 3:1 | dye, 2 cc heparin | 0 | 0.58 | 0.16 | 0.08 | 0 |
| 3:11 | dye, 6 cc heparin | 0 | 0.74 | 0.16 | trace | 0 |
| 3:18 | dye | 0 | trace | trace | 0 | 0 |

The results on dog No. 44 can be interpreted either as variability in dye clearance in the dog, or as liver damage developing during the experimental period. The results on dog No. 38 may be interpreted as showing an effect of heparin on dye clearance or concomitant liver disease, but we feel that the differences were insignificant, because the values were rather low and were similar to the variations seen in repeated control tests in many other dogs.

Ingelfinger (11) has developed a method for determining dye clearance by the liver, the technic of which we thought could be used to answer our problem. He gave an initial i. v. dose of bromsulfalein to saturate the dye storage space, followed by a constant i. v. injection of the dye. By maintaining a constant dye level in the blood, it was assumed that the "transfer rate" of the dye from the blood to the liver could be determined. We have attempted to repeat these experiments. Dogs were kept under nembutal anesthesia for the duration of the experiment. Three such tests were performed on 3 healthy fasting dogs. Hematocrit values and dye concentrations were determined at 15 minute intervals. Control tests with dye only, or with constant i. v. injection of normal saline at the same rate as the dye injections, were performed. The duration of the tests was from 130 to 260 minutes. In the experiments with constant injection of 1 cc of saline per minute hematocrit values varied considerably. Thus hematocrit values at 0, 60, and 120 minutes, in dog 58, were 40.5, 44 and 45 respectively. In dog 84 they were 41.5, 45.5 and 43.7, respectively. Dog 23 was anesthetized and received no infusion, and the hematocrit values were 38.2, 42.4, and 42.8 respectively. In view of these variations, dye concentrations were corrected for hematocrit values. We are not aware that the investigators who used Ingelfinger's method, have corrected dye concentration similarly (10-12).

In only one experiment a fairly constant corrected dye concentration was obtained for a limited period of time, 45 minutes, and in another one for only 30 minutes. In the other experiment no constant levels were obtained for any 2 consecutive 15-minute periods. This type of experiment was not considered suitable therefore, to answer the question of the effect of heparin on dye clearance.

Richards and Cortell (5) believe that an already damaged liver may be affected by dicumarol differently from a normal liver in regard to dye clearance tests. Therefore, we produced mild liver damage with carbon tetrachloride in 2 dogs. It was found impossible however, to obtain a stationary degree of liver damage, i. e. when administration of carbontetrachloride was continued, liver damage increased, and when the drug was stopped, liver function regenerated rapidly as evidenced by blood bilirubin levels. Therefore, this method was not suitable for the evaluation of the effects of heparin on dye clearance.

## SUMMARY

An attempt has been made to evaluate the effects of heparin upon dye clearance liver function tests. A total of 82 bilirubin and bromsulfalein liver function tests without or with administration of heparin were performed on 31 dogs. Variable results were observed with both dyes, on dogs with and without anesthesia. Repeated control dye clearance tests without heparin showed considerable variability in the same animal.

Clearance of bilirubin or of bromsulfalein do not appear to be affected by the injection of large amounts of heparin, thereby indicating the absence of a damaging effect of heparin upon dye clearance by the liver.

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# EXPERIMENTAL CHANGES IN THE DOG'S GALLBLADDER

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BEFORE a planned cholecystectomy is performed, gallbladder function is studied and all clinical factors concerned are evaluated. It happens, however, that patients are operated upon for other conditions, for which there had been no apparent reason to test gallbladder function beforehand. When, at such an operation, nothing is found which may explain the disease except an apparently abnormal gallbladder, the surgeon has to use quick judgment whether or not to perform cholecystectomy. Sometimes gallbladders, which appeared diseased to the surgeon, were found to be normal histologically by the pathologist.

We have been impressed by the variability in the appearance of the gallbladder in normal untreated dogs and in dogs which had been subjected to widely varying experimental procedures. To our surprise, most of these gallbladders were found to be normal histologically. On the basis of these experiences in man and in the dog, we planned, therefore, to investigate which procedures would change the appearance of the gallbladder in the dog, using physiological as well as pathological conditions.

Normal mongrel dogs of both sexes were used. First, the effect of starvation and of feeding on the appearance of the gallbladder were investigated. One group of 8 animals was starved for 24 hours, and another group of 14 animals was fed one pound of commercial dog food each, 1 to 2½ hours before termination of the experiment. At the end of all tests reported in this paper, the animals were sacrificed painlessly. Autopsies were performed immediately on these dogs and on animals that had died.

Next, the effect of chilling was studied. Four animals were anesthetized with i. v. sodium pentobarbital. They were chilled with ice until the rectal temperature had dropped to 30°C., which occurred within 15 to 20 minutes. Penicillin was administered before and after the chilling, because otherwise fulminating pneumonia developed.

Next, the effects of a laxative and of a constipating agent were tested. Croton oil, 5 drops in 30 cc of mineral oil, was administered three times by stomach tube at intervals of four to 10 days. None of the animals showed diarrhea. The dogs were sacrificed 2 to 8 days (average 5 days) after the last dose of croton oil. Tincture of opium, 12 cc, was administered to one dog by stomach tube daily for 41 days, at which time the animal was sacrificed. The dog was constipated severely.

Colchicine and urethane were used to test the effect of the alarm reaction on the gallbladder. Colchicine dissolved in water was given in a single subcutaneous dose of 0.5 mg per kg of body weight (6 dogs). One dog died 5 days after injection, and the others were sacrificed 7, 15, and 57 days respectively after the injection. Two other dogs received a single s. c. injection of 1 mg of colchicine per kg of body weight, and both died within 24 hours. Urethane, 0.5 g. in water, was administered to one dog by mouth daily for a period of 8 days, at the end of which the animal was sacrificed.

We have studied previously the effects of desoxycorticosterone on the liver (1). During this work the gallbladders of a number of dogs appeared abnormal. Therefore, desoxycorticosterone acetate in oil was administered intramuscularly to 7 dogs. A daily dose of 5 mg was given for 5 consecutive days, followed five days later by a dose of 25 mg. Seven to ten days later, the animals were sacrificed. Various pathologic effects of this drug have been described by Selye, but the gallbladder was not mentioned (2).

In previous experiments with anaphylactic shock we had noted changes in the gallbladders in an unusually large number of dogs. Therefore, sensitization was produced in 11 dogs by three subcutaneous injections of .1 g of egg albumin in water, given at intervals of 4 days. One week following the last injection, 0.5 g of egg albumin was injected intravenously. Mild to severe symptoms of anaphylactic shock were observed. The animals were sacrificed 3-5 hours and 1-4 days (average 2.2 days) later. One dog died 4 hours and another one 3 days after severe anaphylactic shock.

In view of a rather high incidence of apparently abnormal gallbladders in the experiments with croton oil or with anaphylactic shock, their combined effects

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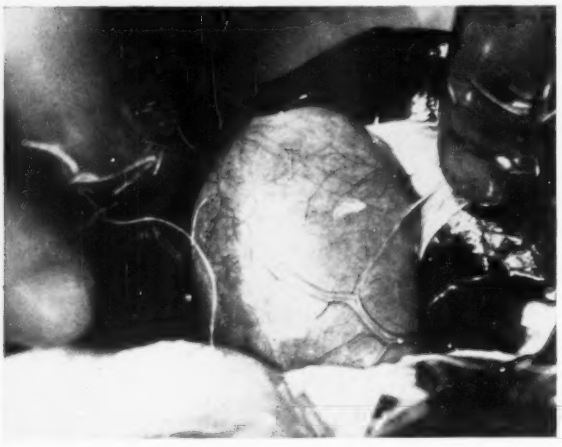

Fig. 1. "Normal" gallbladder of a fed dog.

were tested. Croton oil was administered by mouth to 5 dogs and every administration was followed by a subcutaneous injection of 0.1 g of egg albumin in water. This procedure was repeated 3 times, at intervals of 2 days. An intravenous injection of 0.5 g of egg albumin was given 14 days after the first injection. One animal died in anaphylactic shock. The others showed mild to severe symptoms of shock and were sacrificed 5 hours and 1 to 2 days after the intravenous injection of albumin.

Dakin's solution is known to produce real and rather severe pathologic changes of the gallbladder (3). Therefore, in order to compare the changes in the gallbladder found in the other experiments, with actual cholecystitis in the dog, one animal was given six doses of 30 cc each of Dakin's solution intravenously at intervals of 30 minutes, and was sacrificed 3 days later.

In previous work, we had noted that intraperitoneal application of talcum powder was followed at times by edema of the gallbladder. Therefore, in aseptic operations, talcum powder suspended in normal saline solution was injected into the subserosal lymphatics of the cecum of 5 dogs. The animals were sacrificed 7 to 28 days (average 19 days) after operation.

## APPEARANCE

The appearance of the gallbladders (Table 1) are defined as follows:

*Hyperemia.* The gallbladder had a pink or red appearance, similar to the early stage of an "angry gallbladder," which surgeons consider to indicate an inflammatory condition of the organ.

*Engorged lymphatic ducts.* The gallbladder in the dog is drained by one to three large superficial lymphatic ducts, usually along the longitudinal axis. When filled, they may have a diameter of one to three mm, standing out like cords. The clear appearance of these lymphatic ducts following feeding is unlike the milky appearance of those of the small intestine.

*Lymphatic engorgement of the wall of the gallbladder.* A dense network of small subserosal lymphatic vessels covers the entire surface of the gallbladder. If engorged, they give the gallbladder an appearance of either white elevated patches or of a diffuse white frosted edematous surface, quite different from the normal pale slate-blue color of the organ. This is demonstrated in Figs. 1-3. Lymphatic engorgement denotes one or more such white spots in the serosa of the gallbladder. Their extent would vary from the size of a lentil to nearly covering the surface of the organ. Generalized lymphatic engorgement was similar in appearance, but spread over the entire surface of the gallbladder, so that in no place could one recognize the slate-blue color of the normal organ. Some areas might appear more edematous and would then have a slightly elevated surface.

*Granular mucosa.* The normal mucosa of the dog's gallbladder has a velvety appearance. What we called granular mucosa had a coarse dotted and sometimes reticulated appearance, usually of regular distribution. In some cases it resembled the strawberry gallbladder seen in man.

*Atypical bile.* Normal gallbladder bile in the dog has a typical green color, is of medium viscosity, and does not contain visible mucus or precipitates. Atypical bile contained either separate masses of mucus or mucus threads; it was dark green or black and nearly always contained a coarse, black, sand-like material, which often adhered to the mucosa.

## RESULTS

All gallbladders were well filled, some appeared distended, but none of them were tense. The gallbladders were subjected to manual pressure at autopsy, in order to test for emptying of bile into the duodenum. In all of these tests, a free flow of bile was obtained, although in some cases considerable pressure had to be used.

The dogs that had received colchicine and Dakin's solution (Nos. 4 and 9 in Table 1) manifested toxic effects. The animals in the other series seemed to be

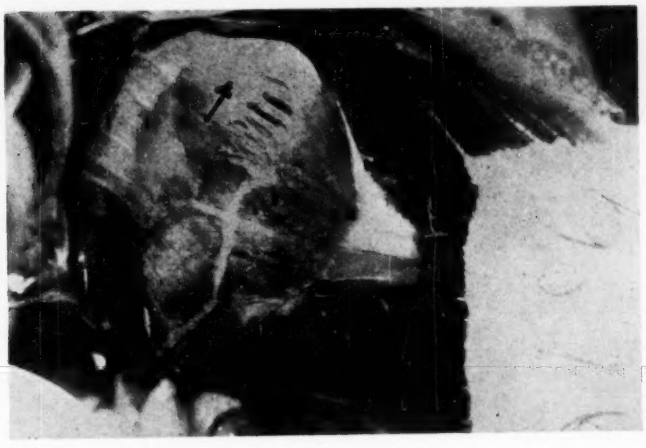

Fig. 2. Patchy lymphatic engorgement (indicated by arrow) and hyperemia of the gallbladder of a dog treated with desoxycorticosterone.

in good health, had no apparent discomfort and had normal appetites, as soon as they had recovered from the various procedures. No animal showed evidence of jaundice, bilirubinemia, of abnormal stools, and in no animal did we find obstruction or dilatation of the biliary ducts.

The gross appearance of the gallbladder following the various procedures is summarized in Table I, demonstrating a rather large number of changes in the appearance of the gallbladder of normal and treated animals.

The incidence of hyperemia of the gallbladder in starved and fed dogs was approximately the same, but we were impressed with the greater degree of hyperemia in the fed dog. In the case of Dakin's solution (No. 9) hyperemia was due to the chemical irritation of the organ (3). In the experiment with talcum powder, obstruction or mechanical irritation by talcum in the lymphatic vessels may explain the high incidence of hyperemia.

Engorged lymphatic ducts were seen more frequently in fed than in starving animals. At the beginning of digestion, the gallbladder empties. As digestion and absorption of food progress, the empty gallbladder fills up with liver bile and begins concentrating it. The latter process may account for engorged lymph ducts. It is possible, that the above explanation holds true for other experimental series (Table I, series 1, 3, 4, 6, and 10), in which engorged lymphatics occurred. Although all animals, except the fed controls, were sacrificed after starving for 24 hours, in a number of stomachs food residues were found, and, in a few, fecal material.

The occurrence of patchy or generalized lymph engorgement was the most striking gross change observed. We had the impression that this, more than any of the other observations, may lead a surgeon to consider cholecystectomy. The incidence of lymph engorgement was higher in starved than in fed dogs. It is possible that, during the post-absorptive state of the intestinal tract, after much of the water has been absorbed from the gallbladder bile, other constituents of the bile are absorbed in higher concentrations than initially, producing irritation and dilatation of the small lymph vessels. The walls of the gallbladders of animals with generalized lymph engorgement of the organ appeared thicker macroscopically than those with hyperemia, engorged lymphatics, patchy engorgement, granular mucosa, or atypical bile. Microscopically, no or little thickening of the walls of the gallbladder was observed, but it is felt that much of the edema was lost during the processing for the histological sections.

In the experiments with croton oil (Nos. 2 and 8) the incidence of general lymph engorgement was rather high. It is known that certain oils can be excreted in the bile (4), and it is possible that croton oil is excreted in the bile and produces an irritation of the lymph vessels of the gallbladder. Lymph engorgement of the gallbladder following treatment with desoxycorticosterone may be related to concomitant damage to the liver (1). In the experiments with Dakin's solution (No.1) and with talcum powder (No. 10) the occurrence of lymph engorgement may be related to chemical and physical irritation (enlarged lymph nodes were seen in the hilus of the liver). In the experiments with anaphylactic shock, with and without croton oil (Nos. 7 and 8), the incidence of lymph engorgement of the surface of the gallbladder was relatively high. It has been reported that the gallbladder may react abnormally in patients suffering from various allergies (5). A mucous plug has been observed, containing eosinophile leucocytes, which obstructed the cystic duct in a patient with known allergy; the resected gallbladder was found to be normal histologically (5). Auer and Krueger (6) have reported similar acute changes in the gallbladder following anaphylactic and histamine shock as we did. Possibly, histamine was liberated by some of our experimental procedures. We have no explanation to offer for a relatively high incidence of edema of the gallbladder in the animals treated with colchicine or urethane.

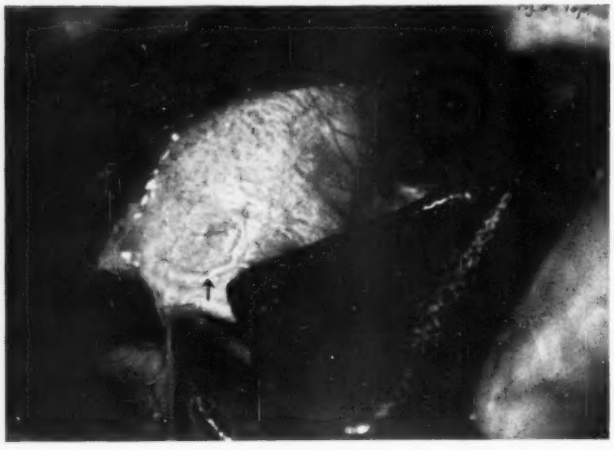

Fig. 3. Extensive lymphatic engorgement of the gallbladder of a fed dog. A dilated large superficial lymphatic duct indicated by arrow.

The meaning of granular mucosa and of atypical bile, which were observed in a number of experiments, is not clear to us. Since the histological findings were normal, these conditions may be due to variations of bile concentration and the state of hydration of the individual animal. For the surgeon, who has to decide at the operating table whether he will or will not extirpate a gallbladder, the findings of atypical bile and granular mucosa would not come into consideration.

Sections of specimen were examined microscopically by Dr. O. Saphir, head of our Department of Pathology, to whom we are greatly indebted. In most cases no pathological changes were found. In a few cases of generalized lymph engorgement slight edema of the subserosa of the gall bladder was seen. However, the pathologist expressed himself explicitly, that in none of the gallbladders was a significant degree of pathology present, that most of them were entirely normal and that the slight changes seen in a few were not of sufficient degree to be called pathological and, would not have justified cholecystectomy in his opinion. The livers were normal histologically except in the experiments with desoxycorticosterone, colchicine and Dakin's solution.

## Discussion

The results of our experiments show that gallbladders which a surgeon may report as grossly

TABLE I

APPEARANCE OF GALLBLADDER FOLLOWING VARIOUS PROCEDURES

| Series No. | Procedure | Total No. of Dogs | Hyperemia | Engorged Lymphatics | Lymph Patchy | Engorgement General | Granular Mucosa | Atypical Bile |
|---|---|---|---|---|---|---|---|---|
| Controls | Starved | 8 | 3 | 4 | 3 | | 3 | 1 |
| | Fed | 14 | 6 | 10 | 1 | 1 | 4 | 2 |
| 1. | Chilling | 4 | 1 | 2 | 1 | — | — | — |
| 2. | Croton oil | 10 | — | — | 2 | 6 | — | 1 |
| 3. | Tinct. Opii | 1 | 1 | 1 | — | — | — | — |
| 4. | Colchicine | 6 | 2 | 1 | 1 | 2 | 1 | — |
| 5. | Urethane | 1 | — | — | — | 1 | — | 1 |
| 6. | Desoxycorticosterone | 7 | 1 | 2 | 3 | 2 | 1 | — |
| 7. | Anaphylactic shock | 11 | — | — | 2 | 5 | 2 | 1 |
| 8. | Anaphylactic shock plus Croton oil | 5 | 1 | — | — | 4 | — | — |
| 9. | Dakin's Solution | 1 | 1 | — | — | 1 | — | — |
| 10. | Talcum powder | 5 | 3 | 1 | — | 4 | 2 | 2 |

pathological are seen in the dog in a variety of normal and abnormal conditions. It is apparent, however, that the incidence of gallbladders with abnormal appearance was higher with a number of experimental procedures. Thus, generalized lymph engorgement of the gallbladder (the most spectacular of the changes of the gallbladder which we observed), occurred in none of the starved and only 7% of the fed animals. Its incidence in treated animals was as follows: croton oil 60%, colchicine 33%, urethane 100% (one dog), desoxycorticosterone 29%, anaphylactic shock 45%, anaphylactic shock and croton oil 80%, Dakin's solution 100% (one dog), and talcum powder 80%.

A few of the conditions, in which we observed a higher incidence of apparently pathological gallbladders in the dog may occur, though to a lesser degree in man; e. g. following chilling, the use of cathartics or other drugs, such as tincture of opium, colchicine, desoxycorticosterone, or in allergic disease.

If our observations in the dog can be applied to man, more attention must be paid to the meaning of gross variations in appearance of the gallbladder. For, from the surgeon's point of view, should such gross changes in the appearance of the gallbladder as we have observed in the dog, be seen at exploratory laparotomy, he would feel justified in regarding it as grossly pathological and remove it. It is well known that the removal of a normal (e. g. in dyskinesia) or of a slightly abnormal gallbladder often is not followed by relief of symptoms and, in a number of cases, the patient may be worse than before. It seems reasonable to assume from the results of our findings that gross changes of the gallbladder found at operation do not indicate the necessity of cholecystectomy, except when they should coincide with definite clinical symptoms and radiographic evidence of gallbladder disease. The greatest danger of unnecessary cholecystectomy might occur in the exploration of the abdominal viscera in the course of definitive surgery elsewhere in the abdomen, when such changes as we have described might be misleading. It is for this reason we feel our observations should be submitted to the surgeon in order to see whether our findings in the dog may apply to the human.

SUMMARY

1. In a number of untreated and treated dogs an abnormal gross appearance of the gallbladder was observed. However, there was no indication of disease of the gallbladder in these animals.

2. The procedures employed in the different groups of experiments were respectively: starving, feeding, chilling, anaphylactic shock, administration of tincture of opium, colchicine, urethane, desoxycorticosterone acetate, Dakin's solution, and the subserosal injection of talcum suspension.

3. The gross appearances of the gallbladders following these procedures were classified as hyperemia, engorged lymphatic ducts, lymph engorgement either patchy or generalized, granular mucosa and atypical bile.

4. All gallbladders, except those of animals injected with Dakin's solution, were normal histologically.

5. In the dog an abnormal appearing gallbladder may be normal. It remains to be investigated whether the results in the dog can be applied to man.

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# STREPTOCOCCI AND DIPLOSTREPTOCOCCI AND THE RESPECTIVE "VIRUSES" IN THE ETIOLOGY AND EPIDEMIOLOGY OF EPIDEMIC RESPIRATORY INFECTIONS AND INFECTIOUS GASTROENTERITIS

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A PARALLEL study was made of the infectivity and antigenicity of streptococci and diplostreptococci isolated from persons ill and from outdoor air during epidemics of respiratory infection resembling influenza and of epidemic gastroenteritis. The outbreaks studied occurred in Ohio and California. They were a part of epidemics that occurred almost simultaneously over vast and widely separated regions of the United States and Canada during the autumn of 1947 and winter and spring of 1948. The severity and type of disease varied greatly in different outbreaks and during the course of the same outbreak from relatively mild so-called "catarrhal fever" to moderately severe influenza with and without symptoms referable to the gastro-intestinal tract. The incidence of bronchopneumonia including so-called "virus" pneumonia and of symptoms referable to the gastrointestinal tract was relatively high. Sharp local outbreaks of uncomplicated gastroenteritis, "intestinal influenza" occurred widely, but more often in relation to epidemics of the respiratory type of infection especially as such epidemics and symptoms in individual cases were subsiding. Symptoms referable to the nervous system were not uncommon during and especially following outbreaks resembling influenza.

The study was made to determine insofar as possible the nature of the infective agent or agents, the relative importance of cultivable streptococci and diplostreptococci and the respective filtrable viruses, the manner of spread over wide areas and the underlying reasons for differences and changes in type of the disease during the course of outbreaks.

From the Laboratory of Bacteriological Research Longview Hospital, Cincinnati, Ohio.
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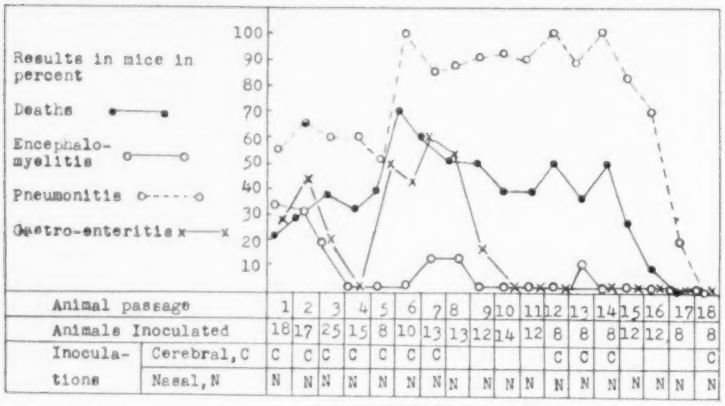
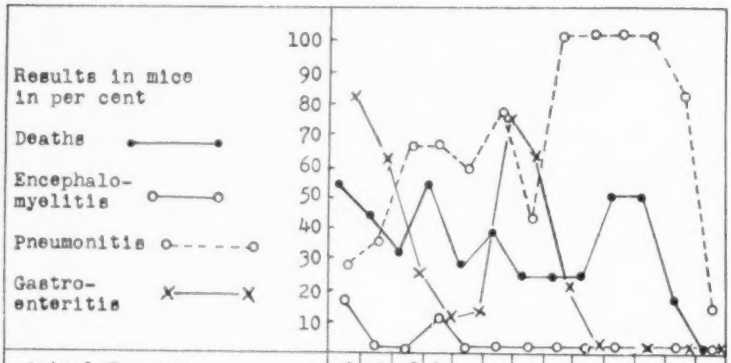
Fig. 1.
Incidence of deaths and of localization in mice following cerebral and/or nasal inoculation of cultures or filtrates of cultures of a streptococcus isolated from outdoor air during a severe outbreak of respiratory infection and gastro-enteritis and of emulsions or filtrates of emulsions of brains, pneumonic lungs and ilia of mice on successive passage.




| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Animal passage | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
| Animals Inoculated | | 18 | 17 | 25 | 15 | 8 | 10 | 13 | 13 | 12 | 14 | 12 | 8 | 8 | 8 | 12 | 12 | 8 | 8 |
| Inoculations | Cerebral, C | C | C | C | C | C | C | C | | | | | C | C | C | | | | C |
| | Nasal, N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

Fig. 2.
Incidence of deaths and of localization in mice following cerebral and/or nasal inoculation of cultures or filtrates of cultures of a diplo-streptococcus isolated from outdoor air during a severe epidemic of respiratory infection and gastro-enteritis and of emulsions or filtrates of emulsions of brains, pneumonic lungs and ilia of mice on successive passage.




| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Animal Passage | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
| Animals Inoculated | | 11 | 26 | 19 | 9 | 7 | 8 | 16 | 4 | 4 | 4 | 4 | 6 | 7 |
| Inoculations | Cerebral, C | C | C | C | C | C | C | | | | | | C | C |
| | Nasal, N | N | N | N | N | N | N | N | N | N | N | N | N | N |

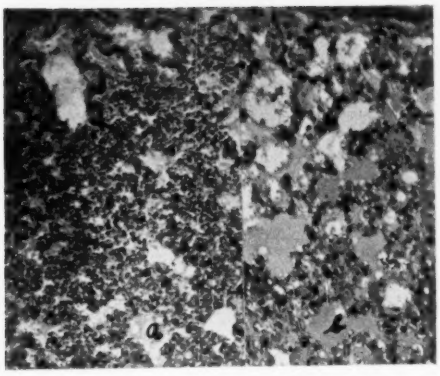



Fig. 3. Photomicrograph of lung of mouse that died of massive hemorrhagic edema of lungs 48 hours after intracerebral and intranasal inoculation of a seven day culture in chick embyro infusion of the streptococcus isolated from outdoor air. Note the peribronchial hemorrhage, in alveoli and exudate in bronchi (a), and the edema, hemorrhage, great dilatation of alveoli, necrosis of alveolar epithelium and capillaries adjacent to and remote from a bronchus (b).

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## METHODS

Cultures of persons ill were from nasopharynx, sputum and stool. Material from the nasopharynx was obtained from behind and above the soft palate with a cotton wrapped wire swab bent to a suitable angle without touching the tongue. The nasopharyngeal swabbing, the sputum and mucus from the stool were suspended in 2 ml of 0.2% gelatin in NaCl or Locke's solution for microscopic examination of Gram safranine stained films for cultures and inoculation of animals.

Cultures from the NaCl solution suspensions were made by plating on blood agar to determine the number and kind of organisms, but for inoculation of animals and agglutination tests, serial dilution cultures were made in dextrose brain broth or alternately in dextrose brain broth and dextrose brain agar, mediums which afford a gradient of oxygen tension and other conditions favorable for the isolation of specifically virulent nonhemolytic streptococci (1). From four to six one hundredfold serial dilutions were made by adding with a 1 ml or 2 ml pipette 0.15 ml of the NaCl solution suspension to the first tube containing 15 ml of dextrose brain broth mixing thoroughly and then transferring 0.15 ml to consecutive tubes without changing pipettes. Pure cultures of streptococci were obtained from the end point of growth of the serial dilutions. The brain broth and brain agar were prepared by adding approximately one part by volume of pieces of fresh or frozen calf or young beef brain to six or seven parts of 0.2% dextrose broth and 0.2% dextrose and 0.1% agar contained in tubes (1.6 x 15 cm) before autoclaving.

Sampling from outdoor air were made by exposing ten wooden applicators, 12 cm in length, in each of a bundle of seven test tubes, 1.5 x 12 cm, with open ends in an improvised holder at the front end of the hood of an automobile for mobile sampling and on improvised weather vanes for stationary samplings (2). The wooden applicators had been soaked in liquid petrolatum, the open ends of the bundle of test tubes were screened with surgical gauze held in place with narrow circular strips of adhesive tape and the bundle wrapped in paper towel or cloth before autoclaving.

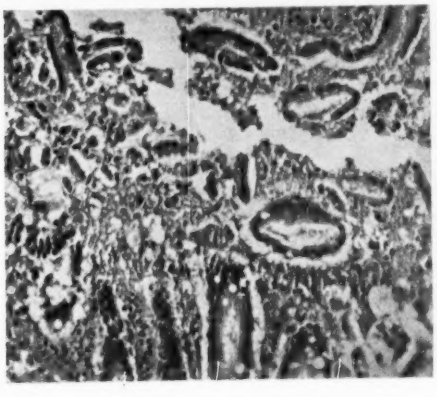

Fig. 4. Photomicrograph of ilium of a mouse that died of gastroenteritis two days after cerebral and nasal inoculation of a seven day culture in chick embyro infusion of the diplostreptococcus isolated from outdoor air during the epidemic referred to in Fig. 4. Note the congestion, edema, cellular infiltration, degeneration and desquamation of epithelium.

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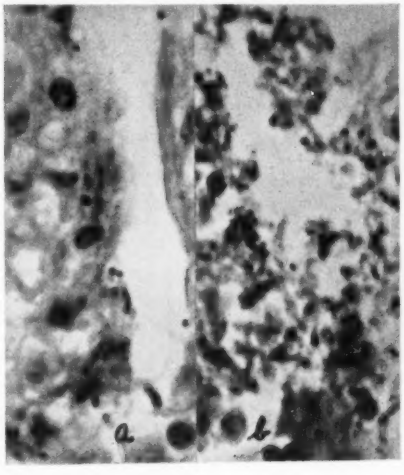


Fig. 5. Photomicrograph of diplococci in the depth of epithelial lining (a), and the large number of swollen diplococci and diplostreptococci in sloughing epithelium (b), in the ilium of the mouse referred to in Fig. 4.

Modified gram stain X 1000

Exposures were made during widely different types of weather, from 10° below zero to 75°F during rains and in sunshine within cities and in the country. Precautions were taken to avoid contamination from the breath or hands of the operator in placing the sterilized sampling units and cultures were made in a nonstacked bacteriological hood. Conditions of the weather were recorded for each sampling. Mobile samplings were made in driving 50 to 200 miles; and stationary samplings by exposure to the air for seven to ten days atop ten foot poles in the ground or atop tall buildings.

Cultures, after exposure, were made by planting from one to five applicators, front end downward, per tube of dextrose brain broth, dextrose brain agar and as a control dextrose broth.

Cultures were made on blood agar and into dextrose brain

Table 1

Incidence of deaths, and of encephalomyelitis, pneumonitis and gastroenteritis in mice following cerebral and/or nasal inoculation of the streptococcus or diplostreptococcus isolated respectively from persons ill and from outdoor air.

| Material inoculated | | | | Strains | Mice | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Inoculated | That died | Percentage in which there developed | | |
| | | | | | | | Encephalomyelitis | Pneumonitis | Gastroenteritis |
| Cultures in dextrose brain broth or chick embryo medium of the | Streptococcus isolated from | Nasopharynx of persons having "influenza" | On isolation | 28 | 79 | 34 | 33 | 96 | 8 |
| | | Outdoor air during epidemics | On isolation | 14 | 98 | 9 | 4 | 69 | 7 |
| | | | After 4 subcultures | 1 | 8 | 0 | 0 | 63 | 0 |
| | Diplostreptococcus isolated from | Stool of persons having severe gastroenteritis | On isolation | 4 | 46 | 22 | 2 | 46 | 78 |
| | | | After 5 subcultures* | | 34 | 41 | 3 | 62 | 15 |
| | | Outdoor air during epidemic | On isolation | 1 | 21 | 5 | 5 | 24 | 71 |
| | | | After 3 subcultures* | | 8 | 0 | 0 | 50 | 0 |
| Control: Dextrose brain broth and chick embryo medium | | | | | 43 | 0 | 0 | 0 | 0 |

*and preservation in dense suspension of glycerol 2 parts and saturated NaCL solution 1 part for six weeks.

Table 2

Incidence of deaths, and of pneumonitis and gastroenteritis in mice following cerebral and/or nasal inoculation of emulsions and filtrates of emulsions of brains, pneumonic lungs and hemorrhagic illia according to mouse passage.

| Material inoculated | | Mouse passages | Emulsions in NaCL solution | | | | | Corresponding Seitz Filtrates | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | No. | Mice inoculated | Percent of mice | | | Mice inoculated | Percent of mice | | |
| | | | | | That died | In which there developed | | | That died | In which there developed | |
| | | | | | | Pneumonitis | Gastroenteritis | | | Pneumonitis | Gastroenteritis |
| Pneumonic lungs | Following inoculation of the streptococcus isolated from outdoor air during an epidemic of gastroenteritis and "influenza" | 2-3-4 | 4 | 16 | 6 | 75 | 0 | 16 | 0 | 13 | 0 |
| | | 5-9 | 4 | 18 | 17 | 100 | 0 | 18 | 11 | 83 | 17 |
| | | 12-15 | 3 | 14 | 50 | 100 | 7 | 14 | 7 | 93 | 7 |
| Hemorrhagic illia | | 9 | 1 | 4 | 50 | 75 | 50 | 4 | 0 | 75 | 0 |
| Pneumonic lungs | Following inoculation of the diplostreptococcus isolated from outdoor air during an epidemic of gastroenteritis and "influenza" | 2-4 | 3 | 13 | 8 | 46 | 23 | 13 | 0 | 0 | 0 |
| | | 6-11 | 3 | 10 | 10 | 80 | 60 | 10 | 0 | 70 | 20 |
| Hemorrhagic illia | | 6 | 2 | 7 | 71 | 29 | 86 | 7 | 0 | 43 | 71 |
| | Following inoculation of the diplostreptococcus isolated from stool* of cases after | 2-3 | 2 | 6 | 100 | 16 | 100 | 6 | 0 | 33 | 83 |
| Control: Emulsions or filtrates of lungs of 43 and ilia of 27 normal mice. | | | | 29 | 0 | 0 | 0 | 50 | 0 | 0 | 0 |

*of persons having severe gastroenteritis

broth or dextrose brain agar of suspensions or emulsions of the brain, lungs and ilia of inoculated and as controls of uninoculated animals. Pieces of brain and lung tissue were mascerated with a small sterile scissors in the mouth of screw capped vials of 4 or 7 ml capacity containing 1 or more ml of sterile NaCl solution and "pebbles." The mascerated tissues were then emulsified by vigorous shaking and part of the emulsions were cultured, part inoculated into mice and part filtered through checked Berkefelt "N" or "V" or "W" filters or Seitz filter pads.

Cultures in dextrose brain broth and chick embryo infusion, filtrates of young and old cultures in chick embryo infusion, emulsions of brain, pneumonic lungs and ilia and filtrates of these were used during successive passages in mice in series. All inoculations were made under ether anaesthesia. Three hundredths ml of the several materials were inoculated intracerebrally far forward into the right frontal lobe and 0.06 ml intranasally. Intranasal inoculations were sometimes repeated within ten or fifteen minutes during a second ether anaesthesia. In most instances only intracerebral or intranasal inoculations were made, but in special instances both methods were used. Relatively young mice weighing from fifteen to twenty grams were inoculated. However, in inhalation and other experiments, both adult and baby mice were used in connection with cultures of the streptococcus and of the diplostreptococcus isolated from newborn infants having acute fulminating gastroenteritis and from outdoor air atop a four story building and a twelve foot pole in the ground during a severe winter epidemic of respiratory and gastrointestinal infection in southern California.

Inoculated mice were observed twice daily and in special instances more often. Those that succumbed were examined for lesions and cultures made as soon after death as possible. Those that survived inoculations for from two to ten days and controls were anaesthetized to death with ether and likewise examined and cultured. Pieces of lungs, of stomach

Table 3
Comparative susceptibility of adult (25 to 30 grams) and baby mice 5 to 10 days old, exposed to the nebulized streptococcus and diplostreptococcus respectively isolated from outdoor air.

| Material inoculated | | | Method of inoculation | Mice | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Type | No. inoculated | Percent in which pneumonitis developed | Percent of lungs yielding the | |
| | | | | | | | Streptococcus | Diplostreptococcus |
| Seven day culture in chick embryo medium of the | Streptococcus Strain 3814 | Isolated from outdoor air during an epidemic of respiratory infection and gastro enteritis after 4 & 3 subcultures* | Intranasally | Adult | 4 | 75 | 75 | 0 |
| | | | Inhalation | | 5 | 20 | 40 | 0 |
| | | | | Baby | 7 | 86 | 86 | 0 |
| | Diplostreptococcus Strain 3815 | | Intranasally | Adult | 4 | 75 | 25 | 75 |
| | | | Inhalation | | 5 | 20 | 0 | 20 |
| | | | | Baby | 5 | 60 | 0 | 60 |
| Control: Sterile chick embryo medium | | | Intranasally | Adult | 4 | 0 | 0 | 0 |
| | | | Inhalation | | 5 | 0 | 0 | 0 |
| | | | | Baby | 8 | 0 | 0 | 0 |

*and preservation in dense suspension of glycerol 2 parts and saturated NaCL solution 1 part for six weeks.

Table 4
Results in mice following cerebral and nasal inoculation of filtrates of chick embryo cultures of the streptococcus and diplostreptococcus isolated from outdoor air and from the stool of persons having gastroenteritis.

| Material Inoculated | | | After at 35°C for, Days | Mice | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Inoculated | That died | Percentage in which there developed | | |
| | | | | | | Encephalomyelitis | Pneumonitis | Gastroenteritis |
| Berkefeld "N" or Seitz filtrates of chick embryo cultures of | Streptococcus isolated from outdoor air | Strain 3814 | 1 | 4 | 0 | 0 | 0 | 0 |
| | | | 7 | 10 | 0 | 40 | 30 | 40 |
| | | | 17 | 7 | 0 | 57 | 86 | 43 |
| | | Strain 3825 | 28 | 3 | 0 | 0 | 67 | 0 |
| | | Strain 3829 | 22 | 4 | 0 | 0 | 50 | 0 |
| | Diplostreptococcus isolated from outdoor air (strain 3815) | | 2 | 4 | 0 | 0 | 0 | 0 |
| | | | 7 | 5 | 0 | 20 | 40 | 60 |
| | | | 17 | 8 | 0 | 0 | 0 | 0 |
| | Streptococcus (3814) & diplostreptococcus (3815) | | 23 | 5 | 0 | 0 | 60 | 60 |
| | | | 107 | 6 | 0 | 0 | 83 | 0 |
| | Diplostreptococcus from stool of persons having gastroenteritis | | 2 | 4 | 0 | 0 | 0 | 0 |
| | | | 23 | 5 | 0 | 0 | 20 | 100 |
| | | | 103 | 2 | 0 | 0 | 0 | 0 |
| Control: Chick embryo medium | | | 3,7,23 | 18 | 0 | 0 | 0 | 0 |

and intestines of test and control animals were fixed in 10% formalin for microscopic study of sections stained with hematoxylin and eosin for lesions and with a modified gram stain for bacteria.

Pure cultures of the streptococcus and diplostreptococcus as isolated from nasopharyngeal swabbings and stool, from outdoor air and from inoculated animals in tubes of dextrose brain broth and in large volumes of 0.2% dextrose broth were centrifuged and the sedimented streptococci were partially dehydrated in dense suspensions, 300 billion to 1000 billion organisms per ml respectively, in glycerin, 2 parts and saturated NaCl solution, 1 part and stored at 5 to 10°C to preserve specificity for subsequent subcultures, for inoculation of animals, for agglutination and precipitation tests and for the preparation of thermal antibody and antigen.

Agglutination tests were made at four fivefold dilutions of 1-10 to 1-1250 of thermal antibody and of antiserums. Thermal antibody was prepared in vitro from the streptococcus and diplostreptococcus and the antiserums in horses with streptococci isolated in studies of respiratory infections and diplostreptococci isolated in studies of epidemic gastroenteritis. The mixtures of antibody and antiserums and respective suspensions were incubated at 48°C for eighteen to twenty four hours when readings were made.

## RESULTS OF INOCULATION OF MICE

The results of inoculation of 185 mice with the streptococcus, of 109 mice with the diplostreptococcus and of 43 control mice are summarized in table 1. The incidence of pneumonitis following inoculation of streptococci from persons having influenza and from outdoor air as isolated and after subcultures was uniformly high and that of gastroenteritis was low. In sharp contrast, the incidence of gastroenteritis following inoculation of the diplostreptococcus from persons having gastroenteritis and from outdoor air as isolated was high, while after subcultures, affinity for the gastro-

Table 5

Results in mice following cerebral and nasal inoculation of filtrates of cultures of the streptococcus and diplostreptococcus in emulsions in NaCL solution of lungs and ilia of normal mice.

| Material inoculated: Seitz filtrates of 10% emulsion in NaCL solution of | | | After at 35° C for, Days | Mice | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Inoculated | That died | Percentage in which there developed | | |
| | | | | | | Encephalomyelitis | Pneumonitis | Gastroenteritis |
| Lungs of 16 normal mice plus | 0 | | 0 | 4 | 0 | 0 | 0 | 0 |
| | 0 | | 12 | 4 | 0 | 0 | 0 | 0 |
| | Streptococcus Strain 3814 | From outdoor air | 12 | 4 | 0 | 0 | 100 | 0 |
| | Diplostreptococcus Strain 3815 | | 12 | 4 | 0 | 0 | 100 | 50 |
| Ilia of same 16 normal mice plus | 0 | | 0 | 4 | 0 | 0 | 0 | 0 |
| | 0 | | 12 | 4 | 0 | 0 | 0 | 0 |
| | Streptococcus Strain 3814 | From outdoor air | 12 | 4 | 0 | 0 | 100 | 0 |
| | Diplostreptococcus Strain 3815 | | 12 | 4 | 25 | 0 | 50 | 50 |
| Pneumonic lung of one mouse that had received filtrate of ileum plus | Streptococcus Strain 3814 | | 12 | 6 | 0 | 0 | 50 | 0 |
| | Diplostreptococcus Strain 3815 | | 12 | 3 | 0 | 0 | 33 | 68 |
| Hemorrhagic ilia (3835) | of five mice following nasal and cerebral inoculation of streptococcus 3814 after 7, 8, and 9 mouse passages | | 0 | 4 | 0 | 0 | 50 | 50 |
| | | | 107 | 3 | 0 | 0 | 0 | 0 |
| Hemorrhagic lungs (3838) | | | 0 | 4 | 25 | 0 | 100 | 25 |
| | | | 107 | 4 | 0 | 0 | 0 | 0 |
| Brains (3837) | | | 0 | 4 | 0 | 0 | 75 | 25 |
| Hemorrhagic lungs of 6 mice following nasal and cerebral inoculation of diplostreptococcus 3815 | | | 0 | 4 | 0 | 0 | 50 | 25 |

intestinal tract diminished as affinity for the lungs increased. The incidence of encephalomyelitis was uniformly low and no lesions were found in the controls. The lesions of the gastrointestinal tract were most pronounced in the ileum and consisted often of extreme congestion and hemorrhage into the wall and lumen.

Emulsions and filtrates of emulsions of pneumonic lungs and hemorrhagic ilia from mice that had received inoculations of the streptococcus or diplostreptococcus, isolated from outdoor air respectively according to mouse passage, were in turn inoculated into 179 mice. The results are summarized in table 2. The incidence and severity of pneumonitis following inoculation of emulsions and filtrates of pneumonic lungs were low during the second, third and fourth passages and were far greater during the fifth, ninth, twelfth and fifteenth mouse passages of the streptococcus. Moreover, the incidence of pneumonitis following inoculation of emulsions and filtrates of hemorrhagic ilia in the ninth passage of the streptococcus was also high, the incidence of pneumonitis and of gastroenteritis following inoculation of emulsions was 75 percent and 50 percent while that to the filtrate was 75 percent and nil respectively.

The incidence of pneumonitis and gastroenteritis following inoculation of emulsions of pneumonic lungs due to inoculation of the diplostreptococcus in the second and fourth mouse passage was relatively low and that following inoculation of corresponding filtrates was nil. The incidence of both pneumonitis and gastroenteritis following inoculation of emulsions and filtrates was far greater in the sixth and eleventh mouse passages respectively. The incidence of gastroenteritis was greatest following inoculation of emulsions and filtrates of emulsions of hemorrhagic ilia produced in the sixth mouse passage containing the diplostreptococcus isolated from outdoor air and in the second and third mouse passages isolated from the stool of newborn infants having gastroenteritis. The total incidence of pneumonitis and gastroenteritis respectively was uniformly greater in mice that received emulsions than those that received filtrates. Control emulsions and filtrates of emulsions of normal lungs and ilia of well mice were without effect. The incidence and severity of pneumonitis and or of gastroenteritis in infants was far greater than in adults in some outbreaks. This was especially true in the epidemic in which the highly virulent streptococcus and diplostreptococcus were isolated from outdoor air. It was thought that the greater incidence and severity in infants might have been due to an inherent greater susceptibility or to a lack of specific immunity from prior exposure to the causative organisms isolated alike from persons ill and from air. Accordingly, the effect of intranasal inoculation and nebulization of adult mice and nebulization in baby mice, of the respective cultures into the cages in which the mice were kept, was studied. Nebulization of 10 ml of culture into cages with sheet iron walls 10x10x10″ and a ¼″ mesh wire door in which the mice were housed was done in a comparable manner twice a day for three days. The mice were anaesthetized to death on the seventh day after the first exposure. The results revealed at necropsy are summarized in table 3. It will be seen that the incidence of pneumonitis and the isolation of streptococci from the lungs was far higher following intranasal than following inhalation inoculation in adult mice and that pneumonitis and isolation of the streptococcus following inhalation was far greater in baby mice than in adult mice. The diplostreptococcus was not isolated from the lungs of mice inoculated with the streptococcus. Gross lesions of the gastrointestinal tract were not found, but isolation of the diplostreptococcus from the lungs of mice that were made to respire the diplostreptococcus was uniformly high. The lungs of control mice were normal and all cultures proved free from streptococci and diplostreptococci.

Table 6
Isolation of the streptococcus or diplostreptococcus from the brain, pneumonic lungs, and ilia of mice following cerebral and/or nasal inoculation of cultures, emulsions or filtrates of emulsions of brains, pneumonic lungs and of ilia showing lesions.

| Material inoculated | | Total cultures, emulsions or filtrates | Animal passages | Material cultured | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Brains | | Pneumonic lungs | | Ilia or contents | |
| | | | | No. | Per cent positive* | No. | Per cent positive* | No. | Per cent positive* |
| Cultures of streptococcus or diplostreptococcus isolated from | Persons ill | 25 | First | 16 | 75 | 179 | 82 | 81 | 72 |
| | Outdoor air | 9 | 2-9 | 24 | 79 | 109 | 79 | 46 | 72 |
| Emulsions of pneumonic lungs | | 7 | 2-12 | 20 | 40 | 106 | 77 | 29 | 72 |
| Filtrates of emulsions of brains, pneumonic lungs or of involved ilia or contents | | 4 | 2-3 | 4 | 25 | 25 | 40 | 11 | 45 |
| | | 5 | 4-8 | 5 | 20 | 21 | 30 | 8 | 25 |
| | | 7 | 9-14 | 7 | 0 | 22 | 18 | 11 | 10 |
| | | 8 | 2-5 | 16 | 13 | 68 | 31 | 30 | 27 |
| Control: Emulsions of brains, lungs, and filtrates of ilia of normal mice | | | | 14 | 0 | 42 | 0 | 11 | 0 |

*for the streptococcus or diplostreptococcus

The occurrence of "pneumotropic" nonhemolytic streptococci (4) and "enterotropic" diplostreptococci (5) and respective filtrable viruses have been reported in epidemic respiratory (6) and gastrointestinal infections (7). The production of pneumonitis and gastroenteritis in this study with cultures of streptococcus and diplostreptococcus with emulsions of pneumonic lungs and hemorrhagic ilia thus produced and with filtrates (Table 2) of emulsions indicate that the cultivable streptococci and diplostreptococci and the respective filtrable viruses may be related. Accordingly, experiments were done to determine whether the respective filtrable agents or viruses might in some way be derived from the cultivable streptococcus and diplostreptococcus and if so extend results of previous studies (3,5). The strains of streptococci and diplostreptococci used in these experiments were so far removed from original source as to eliminate the possibility of the passive transfer of virus which conceivably might have been present in the original inocula. The dilutions of original inocula in the subcultures used ranged from $10^{-24}$ to $10^{-2}$. The production of filtrable agents from the streptococcus and diplostreptococcus was attempted in autoclaved chick embryo infusion which does not turn acid on prolonged growth of these organisms and in 10 percent emulsions in NaCl solutions of lungs and ilia of normal mice.

The results of experiments with filtrates of cultures in chick embryo infusion are summarized in table 4. It will be seen that filtrates of cultures of the streptococcus and diplostreptococcus 1, 2, 2, 17 and 103 days old were without effect and that filtrates of cultures of the streptococcus from outdoor air 7, 17, 22 and 28 days old respectively produced pneumonitis in uniformly high incidence and encephalomyelitis and gastroenteritis in low or no incidence. Filtrates of cultures of the diplostreptococcus from outdoor air and from the stool of persons having gastroenteritis respectively 7, 23 and 23 days old produced gastroenteritis in uniformly high incidence and a filtrate of a culture 107 days old produced pneumonitis in moderately high incidence. No lesions were found in control mice inoculated with the incubated chick embryo infusion.

The results following inoculation of filtrates of uninoculated and inoculated emulsions of lungs and ilia of normal mice and of emulsions of hemorrhagic ilia and lungs of mice following in vivo inoculation of the streptococcus or diplostreptococcus isolated from outdoor air are summarized in table 5. It will be seen (1) that the filtrates of uninoculated, unincubated and incubated emulsions of lungs and ilia were without effect, (2) that pneumonitis developed in all of eight mice receiving filtrates of emulsions incubated for twelve days after inoculation of the streptococcus isolated from outdoor air and that pneumonitis developed in all of eight and gastroenteritis in four of eight mice receiving corresponding filtrates of emulsions incubated for twelve days after inoculation of the diplostreptococcus. Filtrates of incubated emulsions of lungs and ilia inoculated in vivo either with the streptococcus or diplostreptococcus from outdoor air unincubated and incubated for twelve days gave similar specific results while filtrates of materials incubated for one-hundred seven days were without effect.

The isolations of the streptococcus and diplostreptococcus from the brains, pneumonic lungs and ilia of mice that had received cultures of the streptococcus, diplostreptococcus, emulsions of pneumonic lungs or filtrates of emulsions are summarized in table 6. It will be seen that the total number of cultures made was large, 838. Isolations of the streptococcus or diplostreptococcus were uniformly greatest in mice that had received cultures or emulsions. Isolations from brains, pneumonic lungs and ilia of mice that had received filtrates were roughly inversely proportional to the number of animal passages of the filtrates with which the mice were inoculated. Isolations ranged, in the case of two and three passages and nine and fourteen passages, from 25 to 0 percent for the brains; 40 to 18 percent for pneumonic lungs and from 45 to 10 percent for ilia. Cultures of control animals were negative. Cultures in freshly prepared dextrose brain broth of the twenty-four filtrates of emulsions of brains, pneumonic lungs and ilia that were inoculated into the mice yielded the streptococcus or diplostreptococcus in 13 or 54 percent (not shown in table 6) while all cultures in corresponding dextrose broth and on blood agar proved sterile. Moreover, in instances where filtrates were passed consecutively from mouse to mouse, isolations of the

Table 7

Agglutination of streptococci and diplo-streptococci isolated in studies of epidemic respiratory and gastro-intestinal infection by the respective thermal antibody solutions.

| Source of thermal antibody solutions | | | Average percentage of total possible agglutination at fivefold dilutions of 1-20 to 1-2500 of thermal antibody over streptococci, diplo-streptococci and pneumococci isolated in studies of epidemic respiratory and gastro-intestinal infections. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Streptococci from | | | Diplo-streptococci from | | Streptococcus from nasopharynx | | Pneumococcus from sputum, Pneumonia (1,3) |
| | | | Nasopharynx | | Outdoor air | Stool | Outdoor air | Schizophrenia (1,1) | Arthritis (1,2) | |
| | | | Current epidemic (1,22)* | Other epidemics (6,22) | Current epidemic (1,3) | Current (7,4) | epidemic (7,1) | | | |
| Streptococci | Isolated during a study of epidemic of respiratory and gastro-intestinal infections from | Nasopharynx | 81 | 63 | 72 | 24 | 47 | 19 | 31 | 19 |
| | | Outdoor air | 63 | 66 | 63 | 34 | 49 | 31 | 31 | 19 |
| Diplo-streptococci | | Stool | 38 | 50 | 43 | 59 | 59 | 19 | 13 | 19 |
| | | Outdoor air | 50 | 45 | 48 | 57 | 62 | 25 | 25 | 19 |
| Streptococci isolated from nasopharynx of persons having schizophrenia. | | | 32 | 35 | 25 | 11 | 23 | 63 | 25 | 25 |
| Pneumococci Types I II III ss | | | 27 | 40 | 23 | 8 | 23 | 25 | 31 | 69 |
| Control: Dilutions of Glycerol Nacl solution plus $H_2O_2$ after autoclaving | | | 25 | 7 | 16 | 11 | 14 | 13 | 19 | 19 |

*Figures in parentheses indicate the number of suspensions and strains respectively.

streptococcus and diplostreptococcus in dextrose brain broth from the involved tissues became progressively less as was true in previous experiments (1, 6, 7).

Great variation in virulence of different strains of streptococci and diplostreptococci as isolated was found. Moreover, great changes in localizing and disease producing properties of both the streptococcus and diplostreptococcus isolated from outdoor air during a severe combined epidemic were obtained on artificial cultivation and successive animal passage. Since localizations in mice following inoculation of cultures, emulsions and filtrates ran closely parallel, a summary according to successive passages of these materials through mice was prepared. The results for the streptococcus are shown graphically in Figure 1 and those for the diplostreptococcus in Figure 2.

The incidence of pneumonitis (Figure 1) at first was far higher than gastroenteritis following inoculation of the streptococcus. The incidence of pneumonitis increased abruptly during the sixth passage, remained high for eight successive animal passages, then diminished progressively concurrently with the disappearance of epidemic respiratory infection during spring and was lost in the eighteenth passage. The incidence of gastroenteritis was nil in the fourth passage, was moderately high in the fifth, sixth, seventh and eighth passages and then disappeared. Symptoms of encephalomyelitis developed in low incidence in the first three passages, were absent during the fourth, fifth and sixth passages, present in low incidence in the seventh, eighth and thirteenth passages, and were absent in the remaining eight passages. The mortality ran closely parallel with the incidence of pneumonitis.

The incidence of gastroenteritis following inoculation of the diplostreptococcus (Figure 2) was high in the first, second, sixth and seventh passages, was low in the third, fourth, fifth and eighth passages and absent in the ninth, tenth, eleventh, twelfth and thirteenth passages. The incidence of pneumonitis was low in the first and second passages, fairly high in the third, fourth, fifth, sixth and seventh passages and extremely high in the eighth, ninth, tenth, eleventh and twelfth passages and very low in the thirteenth passage. Encephalomyelitis occurred in low incidence only in the first and fourth passages. Mortality at first ran parallel with the incidence of gastroenteritis and later ran roughly parallel with the incidence of pneumonitis and as this occurred, the diplostreptococcus acquired the properties of the streptococcus. The gross and microscopic lesions of lungs and of the gastrointestinal tract resembled those of the spontaneously occurring epidemic diseases and those produced experimentally in previous studies (3,4,5,6). The respective organisms were demonstrated in the lesions produced with cultures and emulsions and were not found in the lesions produced with filtrates nor in the corresponding sections of tissues of uninoculated controls.

## RESULTS OF AGGLUTINATION TESTS

Agglutination experiments with thermal or artificial antibody (3), of natural antibody prepared in the serum of horses, the streptococci and diplostreptococci isolated from persons ill and from outdoor air and control streptococci and pneumococci are summarized in tables 7 and 8. The degree of agglutination is given in percent of the total possible. The agglutination was recorded by the arbitrary scale of 0 to 4 plus. A 4 plus agglutination for each of the four dilutions would equal 16/16 or 100 percent, a total of 7 plus or 7/16 = 44 percent etc. A high degree of specificity of the streptococcus isolated from nasopharynx and outdoor air, and of the diplostreptococcus isolated from the stool and outdoor air during epidemics of respiratory infection and of gastroenteritis was shown by both thermal or artificial antibody (Table 7) and by the immune serums or natural antibody (Table 8). Moreover, the agglutinative titer for the diplostreptococcus isolated from the stool and outdoor air during the epidemic of respiratory infections resembling influenza and gastroenteritis was higher by thermal antibody and by antiserums prepared from the streptococci isolated during the current and other epidemics of respiratory

Table 8
Agglutination by antiserums (natural antibody) of streptococci, diplo-streptococci and pneumococci isolated in studies of epidemic respiratory infection, schizophrenia, arthritis and pneumonia.

| Source of natural antibody | | | Average percentage of total possible agglutination at fivefold dilutions of 1-20 to 1-2500 of antiserums over streptococci, diplo-streptococci and pneumococci isolated in studies of epidemic respiratory infections and pneumonia. | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Streptococci from | | | Diplo-streptococci from | | Streptococcus from nasopharynx | | Pneumococci I II III |
| | | | Nasopharynx | | Outdoor air | Stool | Outdoor air | Schizophrenia (1,1) | Arthritis (1,30) | |
| | | | Current epidemics (1,23)* | Other epidemics (4,539) | Current epidemic (5,1) | Current epidemic (7,4) | epidemic (7,1) | | | (1,3) |
| Serum of horses that had been immunized with | Streptococci isolated in studies of | Influenza and other respiratory infections | 63 | 68 | 56 | 25 | 36 | 0 | 19 | 19 |
| | | Schizophrenia | 13 | 21 | 25 | 3 | 2 | 56 | 0 | 0 |
| | | Arthritis | 38 | 33 | 3 | 0 | 3 | 38 | 75 | 6 |
| | Pneumococci I II III | Pneumonia | 13 | 23 | 19 | 2 | 0 | 13 | 0 | 69 |
| Control: Normal horse serum | | | 19 | 5 | 13 | 3 | 3 | 19 | 0 | 0 |

*Figures in parentheses indicate the number of suspensions and strains respectively.

infection than by antibody prepared with streptococci isolated in studies of schizophrenia and arthritis (Table 8), and the agglutinative titer for the streptococcus isolated in the current epidemic was higher by antibody prepared with the diplostreptococcus than by antibody prepared from heterologous streptococci. This close relationship of the streptococcus and diplostreptococcus and the dissociation of the latter into the former on successive animal passage was reported in a previous study (4).

## COMMENTS AND SUMMARY

The results of a bacteriologic study of nonhemolytic streptococci and of a diplostreptococcus isolated from persons having epidemic respiratory infection and infectious gastroenteritis and from outdoor air are reported.

Great variations in virulence of different strains were noted and great changes in virulence, localizing and other properties of the same strains occurred on artificial cultivation and especially on successive passage through mice of the streptococcus and diplostreptococcus. The different strains of the streptococcus were serologically alike on isolation, remained so after short periods of cultivation and throughout successive animal passages, while the diplostreptococcus dissociated into the streptococcus as affinity for lungs became dominant, on successive mouse passages.

A striking parallelism was found between clinical manifestation as regards incidence and severity of respiratory and gastrointestinal involvement and the experimentally produced lesions of lungs and gastrointestinal tract in mice. Moreover, the changes in clinical manifestations, which occurred spontaneously in human beings during different outbreaks and during the course of the same epidemic, were seemingly due to changes in virulence and localizing properties of the streptococcus and diplostreptococcus since the changes in localization and lesions induced experimentally on successive passage through mice and those that occurred spontaneously were so similar; all of which indicate that the cultivable streptococcus and diplostreptococcus were not only isolable but that they were etiologic and since broadly isolated from outdoor air during epidemics may also have had important epidemiologic significance.

The importance of the cultivable streptococcus and diplostreptococcus was further indicated by: (1) the presence of the respective filtrable agents in pneumonic lungs and hemorrhagic ilia of mice following inoculation of pure cultures, (2) the isolation of the streptococcus and diplostreptococcus at first in relatively high incidence and in decreasing incidence from the lesions produced with filtrates on successive passage and in decreasing incidence from the filtrates that were inoculated on successive passage through mice, and (3) by the production of filtrable transmissible agents resembling "virus" having specific localizing properties, from the streptococcus and diplostreptococcus respectively which were so far removed from original inocula as to eliminate the passive transfer of virus, in cultures in autoclaved chick embryo infusion and in emulsions of lungs and ilia of normal mice at varying periods of growth.

Since nonhemolytic streptococci and diplostreptococci of varying specificity and virulence are commonly present in human beings and other animals, currently considered of little or no importance in the causation of disease, the isolation of "pneumotropic" streptococci from several passage strains of natural influenza virus (3), may not, on the basis of these controlled experiments, the spontaneously occurring viruses of influenza of the common cold (8), of "virus" of atypical pneumonia (9) of infectious gastroenteritis (10) and of pneumonitis in mice (11, 12, 13) be commonly derived from cultivable streptococci or diplostreptococci?

On the basis of the data adduced in this and previous studies (3,4,5,6,7) and the results of studies by others (14,15,16,17), it is suggested that epidemic respiratory infections including the common cold, "virus" or atypical pneumonia and epidemic influenza and epidemic infectious gastroenteritis as they occur seasonally in varying degrees of incidence and severity often have a dual etiology and epidemiology consisting of cultivable specific types of streptococci and diplostreptococci and the respective filtrable viruses and that these seemingly wholly unrelated agents are phasally or mutationally related (6,7,18,19). Moreover, since vaccines prepared from "pneumotropic" streptococci isolated in studies of influenza and other respiratory infections on isolation (15, 20) or from strains whose specificity was maintained by partial dehydration in dense suspensions of glycerine (2 parts) saturated NaCl solution (1 part) have been shown to be harmless, nonsensitizing

and highly effective in prophylaxis (21,22) and in combination with the new nonsensitizing thermal antibody in diagnosis (23) and treatment, their more general use is strongly indicated.


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# THE RELATION OF BILE LOSS TO WATER BALANCE IN THE RAT

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A METHOD of constructing a biliary fistula in rats which allows direct collection of bile was published by Sawyer and Lepkovsky (1) in 1936. Their observation that the animals died within a few days discouraged use of this technique for longer experiments. Harrington, Greaves and Schmidt (2) later found that feeding bile or salt solution to this type of experimental animal by stomach tube prolonged survival for as long as 3 or 4 weeks. Data from a series of rats operated upon in a similar manner, and the effects of therapy on their survival period, weight loss, and bile volume, will be reported here. Since they lack a gall bladder, rats would seem to be ideal experimental animals for the study of unaltered bile direct from the liver. Rats have a natural resistance to infection, a complication which occurs frequently in dogs with biliary fistulas.

As in dogs (3,4), it is possible to construct two types of biliary fistula in the rat, i. e., external and internal. Most of the experiments on external drainage have been acute, such as the effect of choleretics on flow (5,6). The following ingenious techniques have been invented for the study of chronic bile loss. McMaster (7) cannulated the common duct and attached a rubber finger cot. To collect the bile the animals had to be killed. Greaves and Schmidt (8) devised a choledochocolonostomy, which allowed excretion of bile with the feces. This method has the disadvantages of possibly permitting reabsorption of some of the bile from the intestine, and of making collection of bile for analysis difficult or impossible. It has been useful in studying the relation of bile to absorption of the fat-soluble vitamins (9, 10, 11). Sawyer and Lepkovsky described the only technique which they feel fulfills all standards for the production of an ideal biliary fistula. They cannulated the bile duct and connected it to a glass bulb placed in the abdomen of the rat. Bile was collected through an attached tube leading to the exterior of the animal. They found that the animals died in 1 to 4 days with tremendous weight loss, and concluded that bile is indispensable to life. It was dis-

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covered by Harrington, Greaves and Schmidt (2), however, that rats in which bile is eliminated in the urine through an internal fistula survive for months. This method, by which the common duct is connected to the vas deferens, has perhaps become the most popular. Bile constituents may be estimated by chemical separation from the urine, but the bile volume, of course, cannot be accurately measured.

The technique of Sawyer and Lepkovsky allows direct collection and measurement of the volume of bile flow in rats, as does that of Rous and McMaster in dogs (3). There is no possibility of reabsorption or ingestion of bile, with distortion of results. These advantages, and the question of why death occurred so rapidly in animals operated upon in this manner, prompted the experiments below. Also, a method of collecting rat bile for use in studies on fat absorption was desired. It was anticipated that if the survival could be prolonged by a simplified form of therapy, this would permit extension of the period of observations.

## METHOD

Seventy-three Wistar rats (of both sexes) with initial weights ranging between 200 and 520 grams were operated upon. From 60 of these bile was collected in abdominal glass bulbs and in the other 13 combined biliary-pancreatic fistulas were established. The operative procedures will be outlined below. Forty-six of the rats with biliary fistulas, which were fed only the stock diet (footnote 1) and water, were not given any form of therapy. Fourteen were given 2½ per cent glucose in 0.9 per cent saline in addition to their food. The animals with drainage of both bile and pancreatic juice were not given any special treatment.

*Anatomy*: To facilitate the explanation of the techniques used, the arrangement of the bile and pancreatic ducts in the rat will be briefly described. Mann and co-workers (12) have classified domestic animals according to the manner in which these ducts empty into the intestine. Their Group III, including goat, sheep, deer, pocket gopher, mouse and rat, is peculiar in that the pancreatic ducts empty directly into the bile duct. The same arrangement of ducts is found in the ant-eater and duck-bill (13). Thus, a mixture of bile and pancreatic juice enters the intestine. The pancreatic ducts of the Wistar strain of rat used in our laboratories are not paired as reported in animals studied by Morrell (14). Helly (15) describes 2 to 5 large ducts (precursors of the ducts of Wirsung and Santorini) and up to 40 or 50 smaller ducts entering the bile duct. This corresponds with our observations. The distal four-fifths of the bile duct is embedded in the surface of the pancreas (fig. 1), and the pancreatic ducts empty into this portion. Figure 2 illustrates the appearance of the preparation shown in the preceding figure after it was cleared in benzyl-benzoate. The larger pancreatic ducts are now visible as thin, dark branching structures, which follow the pancreatic arterial system. By inserting a cannula at the proximal, or hepatic end of the bile duct, bile alone may be collected and the flow of pancreatic juice left unobstructed. A cannula at the distal, or duodenal end of the duct, will drain both bile and pancreatic juice. If this latter procedure is combined with diversion of bile flow elsewhere, pancreatic juice alone may be collected (16).

Footnote 1. Purina fox chow.

*Technique*: The operations were performed according to a modification of the technique of Sawyer and Lepkovsky. Their apparatus consists of a glass bulb of 6 cc. capacity with two side-arms, one for inflow and the other for collection of bile, a silver or steel tapered cannula, and a specially-made steel needle. Under ether anesthesia and with aseptic precautions, the cannula is inserted into the hemisected bile duct. A ligature tied over a groove in the cannula holds it in place. By means of the special needle, rubber tubing attached to the glass bulb is threaded through a stab wound in the right dorsal body wall of the rat. Tubing connected to the cannula transports bile into the glass bulb. Bile is collected by means of a No. 19 needle inserted through the dorsal tubing. Harrington and associates (2) modified this procedure by placing the bulb between muscle and skin.

In the present series, the above technique was modified by increasing the capacity of the bulbs to 8 to 10 cc., to accommodate the secretion of large (above 200 gm.) rats. It was found that if the bulbs were flattened on both sides, they fitted more readily into the abdomen. Cannulas were made from No. 19 steel hypodermic needles, with a blunt bevel on one end. Towards the conclusion of the experiments it was found that use of flexible plastic cannulas of fine diameter resulted in fewer postoperative complications secondary to penetration of the duct. Plastic tubing connected the cannula to the bulb. In those experiments in which it was desired to obtain bile unmixed with pancreatic juice, the bile duct was cannulated near its site of origin from the various hepatic ducts. The cannula was inserted at the duodenal end of the bile duct when it was desired to collect not only bile, but also pancreatic juice. The special forceps of Haas and Goldblatt (17) proved an invaluable aid in performing many of the cannulations.

*Postoperative Care*: The animals tolerated the apparatus without obvious discomfort, but sometimes chewed off the external stopper after a few days. They were kept in individual cages and fed the stock diet and water *ad libitum*. Therapy in the form of 2½ per cent glucose in 0.9 per cent saline (placed in the water bottle) *ad libitum* was instituted in some cases on the day of operation. Attempts to feed bile or other fluids by stomach tube were abandoned when it was found that this procedure repeatedly dislodged the cannula from the bile duct. Bile was collected twice daily, at 10 a.m. and 6 p.m. Occasionally overflow of fluid from the dorsal tubing occurred. This was most frequent with the combined biliary-pancreatic fistulas, but quantitative recovery was obtained with almost all biliary fistulas. At autopsy the animals

Fig. 1. Bile duct injected with India ink (Wistar rat). It is embedded in the surface of the pancreas. The pancreatic ducts, which empty into the bile duct, are not visible. x 3.

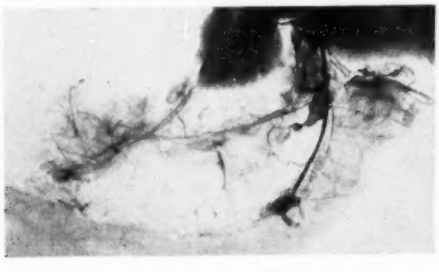

Fig. 2. Same preparation (Fig. 1) after clearing in benzyl-benzoate. The pancreatic ducts follow the arteries closely, and are now clearly visible. x 3.

were examined to determine the cause of death and the patency of the cannula was checked. Paraffin sections of formol-fixed blocks of liver, kidney and pancreas were stained with hematoxylin and eosin. In selected cases, sections of liver were stained to demonstrate connective tissue and sections of pancreas to differentiate the various cells of the islets. If biliary obstruction occurred, evidenced by jaundice, cessation of bile flow and choluria, the animal was killed by ether anesthesia and pneumothorax.

## RESULTS

*Cause of Death*: For the data in table 1, 24 animals were chosen which exhibited no signs of biliary obstruction or other complications during the period of observations (2 to 14 days). Twenty of them were of the biliary fistula type; 10 received fluid therapy and 10 did not. In the other 4 there was complete drainage of both bile and pancreatic juice; no special fluid was given to these. In calculating weight loss and bile volume, the only data used were those recorded during that period in which the rat was free of biliary obstruction. It may be seen that complications involving the apparatus, rather than metabolic disturbance, accounted for most of the deaths. Biliary obstruction due to plugging of the cannula or tubing was the most common complication. In this case the animal was killed before the late effects of bile deprivation occurred, so that microsections free of evidences of postmortem change might be obtained. Bile peritonitis following dislodgement of the cannula also occurred (3 rats). As death was most frequently produced by these postoperative accidents, therefore the *maximum* effect of the therapy in prolonging the period of survival in the presence of free bile flow could not be ascertained. Nevertheless, the survival periods and other data obtained *before* onset of complications seem significant. Animals from which all bile was lost via the fistula, and which had not received any form of replacement therapy, survived for an average of 6 days before complications occurred, whereas those given glucose in saline solution survived 9 days. Those with drainage of both bile and pancreatic juice died in 4 days. Among those of the first group which were not killed because of biliary obstruction, death occurred in an average of 4 days, from dehydration and no other apparent cause. In the second group, fluid therapy prevented death from "bile lack" but the rats either died from, or were killed because of complications. Three of the four animals in group III (table 1) died from dehydration.

*Weight Loss and Bile Volume*: The average daily weight loss and bile volume in all groups paralleled the amount of dehydration present, the latter being estimated as described below. Rats not given access to the glucose in saline solution lost an average of 14 grams of body weight daily, and secreted 2.7 cc. of bile per 100 gm. body weight. Those given this fluid lost only 5 grams daily, and secreted on the average 3.5 cc. of bile. Animals with drainage of both bile and pancreatic juice lost 19 grams daily, secreted 5.4 cc. of fluid. This latter figure is inaccurate, because of overflow of digestive juice from the bulb in three of these rats.

*Postmortem Findings*: At autopsy, varying degrees of dehydration were found in the rats not given therapy, whereas the tissues of those given fluid seemed normal in this respect. The tissues of dehydrated animals were sticky and lusterless. The serosal surfaces had lost their usual smooth slippery touch, and peritoneal fluid was diminished or absent. The capsules of liver and spleen were frequently wrinkled. Emaciation and wasting of subcutaneous and mesenteric fat were usually present. In many cases the glass bulb had become surrounded by a plastic membrane, but only in three rats was there a purulent peritonitis. In the three animals with bile peritonitis following dislodgement of the cannula from the bile duct, fat necrosis, pancreatitis, and a diffuse inflammatory reaction of the serosal surfaces were noted. In all the animals with evidences of biliary obstruction, histological sections showed the changes typical of biliary cirrhosis. In figure 3 (liver of rat 35, killed after 5 days of biliary obstruction), proliferation of bile ducts and fatty changes in the parenchymal cells are evident. The animals with combined biliary-pancreatic fistulas exhibited all signs of extreme dehydration of the tissues. In the sections from the pancreas of rat 8 (fig. 4), the acini are enlarged and crowded together. They contain large numbers of secretory granules, an appearance suggestive of a storage phase. In many areas the acini had apparently regressed into primitive undifferentiated ducts.

## DISCUSSION

*Fluid Balance and Bile Loss*: From the foregoing

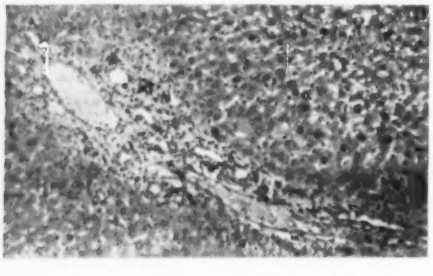

Fig. 3. Liver from rat 35, 5 days after obstruction in the biliary fistula. Note the proliferation of bile ducts and fatty changes in the hepatic cells. No focal necrosis was present. Hematoxylin and eosin stain, x 80.

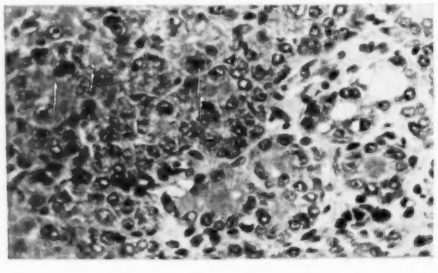

Fig. 4. Pancreas from rat 8 with combined biliary-pancreatic fistula. There is disorganization and increased granulation of the acini. Some appear to be regressing into collecting ductules. Hematoxylin and eosin stain, x 300.

it is apparent that bile metabolism plays an important role in fluid balance in the rat. The animals with external biliary fistulas given food and water exhibited almost three times the weight loss of those given food and 2½ per cent glucose in saline. Food intake following operation was not measured, and it was not attempted to assess the relative effect of this factor on the weight loss. The calculated caloric value based on the amount of glucose ingested (about 1 gm. daily) could only have been sufficient to increase the weights of the treated animals slightly. Therefore, the decrease in weight of the group not given therapy was probably due to dehydration and salt deprivation, as well as to reduced food intake. The "tremendous loss of weight" noted by Sawyer and Lepkovsky in their series was probably caused by the same factors. The average loss of 5 grams exhibited daily by the well-hydrated rats could be accounted for by impaired absorption of food in the absence of bile or by postoperative anorexia. The wide range of weight loss by members of the untreated group (4 to 23 gm. daily) can be explained by individual variations in food and water intake. For example, rat 25 ate and drank well, preventing marked weight reduction. It was significant that the progressive declines in weight were halted whenever biliary obstruction prevented drainage of bile. Animals of the second group, supplied with glucose in saline solution, lost 2 to 9 grams daily, and one of these (rat 28) even gained slightly (1 gm.). The third group (combined biliary-pancreatic fistula) showed the greatest diminution in weight. Here the loss of not only bile but also pancreatic juice probably enhanced the disturbance in water balance and absorption. Acidosis from loss of these alkaline fluids was very possibly an added factor.

The 2½ per cent glucose in 0.9 per cent saline was chosen for therapy on the following grounds: 1) it would replace fixed base and chlorides lost in the bile; 2) it would supply calories to combat weight loss due to postoperative anorexia; 3) it would stimulate drinking and thus help to correct dehydration. Although individual animals drank as much as 100 cc. daily, the intake averaged less than 50 cc. The volume of fluid consumed by the animals offered glucose in saline (group II) was greater than that by the rats given only water (group I). Sawyer and Lepkovsky noted reduced water intake and urine volume in their experimental animals. Since the inorganic salt content of fistula bile is 0.8 per cent (18), in order to maintain fluid balance the animals of group II would have had to drink approximately the same amount of saline solution as the volume of bile secreted. This actually appeared to be the case, for little loss in weight occurred in this group. It is apparent that the ideal replacement for bile lost via a fistula would be bile itself. But attempts to feed a separate series of animals diluted rat bile or bile salts in solution from the water bottle were unsuccessful, for they would drink only small amounts of these bitter mixtures. Feeding by stomach tube, as noted earlier, often dislodged the cannula from the bile duct.

Hepatic bile is approximately isotonic with blood plasma. Both its fixed-base and chloride levels correspond closely with those of plasma (19). Changes in the concentrations of these elements in bile are determined by the osmotic pressure of the blood (20). One function of a gall bladder is to concentrate the bile by absorption of chlorides and water (21). The rat, without a gall bladder, lacks this reabsorptive mechanism. It has been found by Gorham and Ivy (13) in studying the evolution of gall bladder function, that the efficiency of the concentrating apparatus in different vertebrate species varies inversely with the bile volume. The bile of small rodents is thus relatively dilute, for it contains a smaller percentage of solids than the bile of other animals (22). Because of the large volume of bile, the total solids excreted per unit weight are the same. This explains the rapid dehydration of rats with biliary fistulas. Water and salts would have to be withdrawn from the tissues to replace that lost in the bile. Administration of saline would allow replacement of fixed base, chlorides, and water, resulting in fluid balance.

*Survival Period with Bile Loss:* In contrast with Sawyer and Lepkovsky's series, only 2 of 10 rats in our experiments not given therapy (group I) died within 1 to 4 days. One large rat (25), in spite of a continuous flow of bile, survived 14 days, after which biliary obstruction supervened. In the experiments of the above authors, the bile duct was cannulated at its duodenal end, thus draining not only the bile but also the total pancreatic secretion. Their results, therefore, apply to combined biliary-pancreatic fistulas, rather than to biliary fistulas alone as is stated. Their data must be interpreted in this light, and should only be compared with the data from similar animals in group III (combined biliary-pancreatic fistulas) of our series. These rats died in an average of 4 days. The average daily weight loss of Sawyer and Lepkovsky's 6 rats, 17 grams (calculated from their table), agrees well with the figure of 19 grams for our group III. The survival period of rats with external loss of bile was quite variable. It is undoubtedly influenced by many factors, such as amount of salt in the food (footnote 2), body weight and reserve of tissue fluid, operative shock and blood loss, infection, etc. Certain rats, notably the smaller ones (rats 58 and 60), died within a few days. But the majority survived at least 5 days. In most animals (14 out of 24), drainage of bile was impaired by obstruction or leakage at the time of death. Therefore, the data derived from the present series do not provide information concerning the maximum length of the survival period of rats with continual and complete external loss of bile.

*Pancreatic Fistulas:* The cause of death in animals which have lost large amounts of pancreatic juice alone is obviously a separate question, and is being investigated at present. Work in progress (16) indicates that rats with external drainage of pancreatic juice, accompanied by maintenance of internal flow of bile into the intestine, die within 10 days with symptoms of dehydration and acidosis. Most published reports of the effect of loss of digestive juice on acid-base balance have dealt with pancreatic or intestinal, rather than biliary, fistulas. It has been proven by many investigators (23, 24, 25, 26) that dogs with loss of pancreatic juice die in 5 to 8 days. Chemical studies indicate that death is due to dehydration with loss of fixed base, although there may be some other unknown vital factor.

*Salt Deprivation and Bile Loss:* It is considered by most authors (27, 28, 29) that bile is essential to life. Dogs with external biliary fistulas usually die within a few months, but survival may be extended to as long as 4 years by administration of bile by mouth (29). Scott (30) succeeded in keeping 4 dogs with internal biliary fistulas alive for 3½ years by injecting vitamins A, D and K. He postulated that the necessity of bile for life

Footnote 2. The stock diet employed contained 0.5 per cent salt.

is associated with adequate absorption of the fat-soluble vitamins. Boyd and associates (31) felt that salt deprivation secondary to bile loss might be the factor which caused death in dogs with external fistulas. These investigators found that the output of organic salts in the bile increases with the duration of the fistula. Guinea pigs with loss of bile die within a few days (22), probably due to the same factor. Andrews and Bissell (32) are apparently the only authors to follow the acid-base equilibrium by means of blood chemistry in dogs with chronic biliary fistulas. These workers concluded from determinations of blood carbon dioxide and chlorides in 8 dogs that disturbance in acid-base balance does not play a fundamental role in cachexia cholepriva. Perhaps even the 80-day period employed for these observations is too short for marked changes in blood chemistry to occur.

*Comparison of External and Internal Biliary Fistulas*: In contrast with the rapid exodus of rats with external fistulas, animals with *internal* biliary fistulas of the vas deferens type survive for 3 to 5 months (2, 33) (footnote 3). Dogs with internal cholecystnephrostomies (34, 35) survive considerably longer than dogs with external drainage of bile (3, 29, 31). Whereas dogs of the Rous-McMaster type lose 1 to 1.5 kgm. per month (36), dogs with internal renal fistulas maintain their weight fairly well (4). No adequate explanation for this great difference in survival period and weight loss has been demonstrated, and it is usually ascribed to infection involving the site of the external fistula. It is possible, however, that in the case of the internal type of fistulas, reabsorption of water, of bile salts and of inorganic salts, separately or in combination, takes place in some portion of the urinary tract. In support of this latter contention, it has been demonstrated that there is good absorption of certain drugs from the ureter and renal pelvis in dogs (37, 38). Macht (39) has shown that there is efficient absorption of drugs from the urethra of dogs. The bladder absorbs salt and water poorly (48). In addition, the remaining portion of the gallbladder in the animals of the renal fistula type might continue to absorb water and chlorides. The same general statement can be made concerning rats with choledochocolonostomies, which live for 3 to 4 weeks (9). It is well-known that considerable absorption of water and salts takes place from the colon.

*Biliary Obstruction and Fluid Balance*: Rats in which the common bile duct has been ligated above the entrance of the pancreatic ducts usually die within 2 to 12 weeks (41, 42). Weight loss in these animals is very slight, and the preoperative weight may be maintained or improved (42). Obstruction of the bile duct usually causes death in dogs within 3 to 4 months (43, 44); the longest reported survival is 16 months (45). The animal's weight may be maintained in spite of lack of bile. Death in both species is usually due to hemorrhage, hepatic insufficiency, or duodenal ulcer. There is no external loss of inorganic salts, and therefore little systemic disturbance in acid-base balance. This evidence might again be regarded as supporting the thesis that the profound weight loss in animals with fistulas is due mainly to the disturbance in fluid and salt balance, rather than to any specific nutritional deficiency secondary to absence of bile.

Footnote 3. One rat of this type operated upon by us survived 7 months.

*Bile Volume in Rats*: Volume of bile secreted by rats has been shown by the present experiments to depend on the degree of hydration, also on the amount of pancreatic juice added to the bile by pancreatic ducts draining into the bile duct above the site of cannulation. Analysis of the data submitted by other investigators offers further support for this latter contention. In the experiments of McMaster (7), the site of cannulation was above the pancreatic ducts. He obtained 1.5 to 6.5 cc. of bile per 100 gm. of body weight daily over a period of 1 to 16 days. Values given in Sawyer and Lepkovsky's table (1) for 6 rats followed for 48 hours amount to between 4 and 6 cc. per 100 gm. Krayer (46) also finds 4 to 6 cc. of secretion daily, multiplying from values obtained over a 6 hour period. Both of the latter estimations are increased (perhaps doubled) by pancreatic juice, since the bile duct was cannulated near the duodenum (footnote 4).

Bile volume in our series ranged between 1.2 and 5.3 cc. per 100 gm., depending on the degree of hydration. Rats which received fluid in the form of water only (group I) and were dehydrated by bile loss, secreted from 1.2 to 5.3 cc. per 100 gm. of body weight. In only a few animals was it observed that the daily yield on the last few days before death was less than that during the first postoperative days. Apparently in the rat cholopoiesis by the liver is carried on at the expense of tissue fluids, despite increasing dehydration. The rats which received glucose in saline solution (group II) secreted from 1.6 to 4.6 cc. of bile per 100 gm. of body weight. These animals were presumably in satisfactory water balance. The average volume for this group (3.5 cc.) was greater than the comparable value for the dehydrated rats (2.7 cc.). This suggests that the state of fluid balance controls the amount of bile flow to a large extent. On days when the animals ingested a large amount of glucose in saline it was noted that the bile volume was accordingly increased. One rat (not included in the table) which had been previously dehydrated by drainage of bile and which had secreted only about 8 cc. daily, began to produce 16 cc. of bile when allowed 2½ per cent glucose in saline in place of water. The importance of this relationship has perhaps not received enough attention in both physiological experiments and clinical practice. The changes in bile volume found by Rous, McMaster and Broun (47) in dogs, due to factors such as increased temperature, operation and exercise, should probably be re-evaluated in terms of the accompanying fluid loss. Of equal importance in treating with choleretics the "bile stasis" which accompanies surgery or disease of the biliary passages, is the maintenance of fluid intake.

The average volume of bile in our rats maintained in good fluid balance (3.5 cc.) checks well with McMaster's figure (3.6 cc. per 100 gm.) (7). One factor which may have decreased our values is the interruption of the enterohepatic circulation of bile salts. Drainage of bile would produce a deficiency in bile salts circulating through the liver. This might reduce the endogenous choleretic effect, and decrease the bile volume. Therefore, average daily bile flow from an acute fistula would be expected to be more than that from a chronic fistula. As mentioned before, however, in most animals bile volumes collected during the first few days from rats given fluid therapy were no greater than values for the last few days before death. In those animals not given therapy, only 3 out of 10 exhibited a terminal decrease in bile flow (rats 8, 20 and 58). Since the average bile flow yielded by rats given no therapy was only three-fourths of that secreted by rats given 2½ per cent glucose in saline, this decrease can be accounted for by dehydration. Another factor which may influence bile flow in rats with "artificial gall bladders" is back-pressure from bile collected in the bulb. Halpert (48) found that increased hydrostatic pressure reduced the rate of flow in rabbits. The hydremia produced by intravenous injection of large quantities of salt solution does increase the secretion of bile (49), but the relatively small amounts of saline ingested by the rats in the present series probably had little effect. Water in amounts normally ingested has no effect on output of bile (50).

Footnote 4. Dr Krayer in a personal communication states that the cannula was pushed well up the bile duct, but that contamination of bile with pancreatic juice probably did occur.

TABLE I

SUMMARY OF SURVIVAL PERIOD, WEIGHT LOSS, AND BILE VOLUME IN RATS WITH EXTERNAL LOSS OF BILE

| No. of rat | Sex | Preoperative wt. *grams* | Survival period with good flow *days* | Complications | Cause of death | Av. daily wt. loss *grams* | Av. daily bile vol. *cc/100 gm.* |
|---|---|---|---|---|---|---|---|
| GROUP I. Biliary fistula, not given special therapy. | | | | | | | |
| 6 | M | 485 | 8 | Biliary obstruction | Peritonitis | 4 | 2.3 |
| 7 | M | 520 | 6 | None | Pneumonia | 23 | 3.0 |
| 8 | M | 478 | 5 | Biliary obstruction | Dehydration | 21 | 2.7 |
| 10 | M | 470 | 5 | None | Dehydration | 23 | 2.4 |
| 20 | M | 435 | 5 | Dehydration | * | 18 | 1.5 |
| 25 | M | 520 | 14 | Biliary obstruction | * | 8 | 3.5 |
| 34 | M | 402 | 6 | Cannula penetrated duct | Bile peritonitis | 7 | 3.0 |
| 35 | M | 498 | 5 | Biliary obstruction | * | 8 | 1.2 |
| 58 | F | 232 | 3 | None | Dehydration | 14 | 5.3 |
| 60 | F | 234 | 2 | None | Dehydration | 15 | 2.3 |
| Average | | 427 | 6 | | | 14† | 2.7‡ |
| GROUP II. Biliary fistula, given 2½ per cent glucose in 0.9 per cent saline. | | | | | | | |
| 27 | M | 432 | 9 | Wound infection | Peritonitis | 6 | 3.3 |
| 28 | M | 514 | 11 | Plastic peritonitis | Peritonitis | -1 | 3.3 |
| 30 | M | 312 | 4 | Biliary obstruction | * | 5 | 4.8 |
| 46 | F | 282 | 5 | Biliary obstruction | * | 4 | 3.3 |
| 47 | F | 320 | 23 | Biliary obstruction | * | 2 | 1.6 |
| 48 | F | 360 | 7 | Biliary obstruction | * | 2 | 2.4 |
| 49 | M | 348 | 9 | Bile peritonitis | * | 6 | 3.8 |
| 50 | M | 354 | 11 | Cannula out | Bile peritonitis | 6 | 4.6 |
| 51 | M | 410 | 6 | Cannula out | * | 6 | 4.1 |
| 52 | M | 390 | 7 | Cannula out | * | 9 | 3.3 |
| Average | | 372 | 9 | | | 5† | 3.5‡ |
| GROUP III. Combined biliary-pancreatic fistula, not given therapy. | | | | | | | |
| 2 | M | 338 | 2 | None | Dehydration | 30 | 5.1** |
| 3 | M | 330 | 6 | Obstructed tube | * | 16 | 4.7 |
| 6 | M | 280 | 3 | None | Dehydration | 14 | 7.2** |
| 8 | M | 272 | 4 | None | Dehydration | 14 | 4.4** |
| Average | | 305 | 4 | | | 19 | 5.4 |

*Killed before death occurred, to obtain sections free from postmortem changes.
**Values inaccurate, due to overflow of fluid from bulb.
†The probability that the observed difference between the average weight losses of the two groups occurred by chance is calculated to be 0.000145.
‡The probability of occurrence of the difference between average daily bile volumes by chance is 0.089.

*Why is Bile Essential to Life?* The function of bile as a reservoir for alkali has been well-recognized in the past. In recent years increasing attention has been devoted to its role in nutrition, especially in regard to absorption of the fat-soluble vitamins. However, as postulated by Boyd *et al* (31), the immediate necessity of bile for life may lie in its ability to influence salt and water balance. The evidence reviewed in this paper strongly indicates that patients with biliary fistulas should receive adequate therapy to replace the electrolytes and water lost in the bile. This is especially important following removal of the gall bladder.

## SUMMARY AND CONCLUSIONS

1. The previously-published methods of constructing biliary fistulas in rats have been reviewed, and the arrangement of the bile and pancreatic ducts in this species briefly described.

2. A modification of one of these techniques (1) was employed to study the survival period, weight loss, and bile volume of rats with continued external drainage of bile.

3. Most of the weight loss which occurred could be prevented and the survival period prolonged by replacing the animals' drinking water with 2½ per cent glucose in saline.

4. Bile volume in rats depends on the degree of hydration present. Figures obtained by other investigators have frequently been increased by contamination of bile with pancreatic juice.

5. Consideration of the data obtained emphasizes the importance of bile metabolism in body fluid and salt balance.

6. It is hoped that the "artificial gall bladder" technique of Sawyer and Lepkovsky, in conjunction with the special therapy mentioned above, may be useful in further studies of bile metabolism.

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# THE MANAGEMENT OF PROFUSE BLEEDING FROM PEPTIC ULCER

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WHEN a peptic ulcer begins to bleed severely, it becomes a matter of real concern to the patient and to his physician. Immediate treatment to bring the hemorrhage under control is a matter of dire necessity if we are to prevent the patient's going into shock or exsanguinating himself. It is for this reason that we are reviewing our treatment of 68 cases of bleeding peptic ulcer seen at Montefiore Hospital in the period 1936 through 1948 and outlining our management in specific detail of this type of case.

## DIAGNOSIS

The diagnosis of bleeding peptic ulcer rests on these tenets: 1. The history of antecedent ulcer. 2. Signs of gastro-intestinal bleeding. 3. Constitutional signs of hemorrhage.

The patient frequently has a previous positive diagnosis of peptic ulcer. Even if he has not sought medical aid, he will give a history of epigastric pain, food relief, or nausea. With the onset of severe hemorrhage, pain frequently disappears. This is thought to be due to the loss of tonus of the gastro-intestinal musculature subsequent to the anemia and shock. Hematemesis and or melena are positive evidence of gastrointestinal bleeding. One or the other or both are usually present in cases of bleeding peptic ulcer. Although melena without hematemesis is usually seen with post-pyloric bleeding, it is occasionally seen in bleeding from the esophagus or stomach. Ratnoff and Patek (1) report a number of cases of rupture of esophageal varices in which melena was present but in which no hematemesis occurred. Usually bright

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red blood in the stool is indicative of hemorrhage below the ileo cecal valve, while tarry stool is seen in lesions proximal to it. However, very massive hemorrhage with hypermotile bowel may result in red colored stool. The amount of bleeding necessary to produce tarry stool is not great. Daniel and Egan (2) have experimentally produced tarry stool by feeding less than 100cc of blood to normal individuals. After a single hemorrhage, tarry stool will persist up to five days. Schiff (3) and his associates fed normal subjects 1000cc of blood by tube and noted tarry stool from three to five days. However, a positive chemical test for occult blood can be obtained for three weeks following a single hemorrhage (4).

While bright red vomitus is the usual finding in ulcer and "coffee grounds" vomitus is most often found in cancer, this finding is not absolute and often the vomitus in ulcer will be "coffee grounds"-like and bright red blood may be vomited in case of cancer.

If bleeding is very slow, the onset of constitutional signs of hemorrhage may be gradual and lead only to weakness and chronic hypochromic anemia. If, however, there is a large brisk hemorrhage, the onset is rapid and the signs are severe, even to the point of shock with the classical signs of weakness, sweating, faintness, giddiness, pallor and tachycardia. The symptoms are related not so much to the total amount of blood lost as to the rapidity of the loss.

## DIFFERENTIAL DIAGNOSIS

There are several other conditions causing gastro-intestinal bleeding with hematemesis and melena which must be differentiated from peptic ulcer. Next in frequency as a cause of hematemesis, is rupture of esophageal varices. These are almost invariably caused by portal obstruction subsequent to hepatic cirrhosis and secondary venous obstruction. In some institutions, particularly municipal, taking care of large numbers of alcoholics and seeing large numbers of cirrhotics, ruptured esophageal varices may account for as many as 30-35% of the cases of hematemesis. In our hospital it was present in only 3% of cases of massive hematemesis. Occasionally these varices develop early in the course of a cirrhosis and diagnosis is difficult. Roentgenogram will show the typical notching as a "string of pearls"—appearance of the lower esophagus. The varices can be directly visualized by esophagoscopy. In the later stages, the classical finding of ascites, jaundice, hepatomegaly and splenomegaly and spider angiomata clarify the picture and bromsulfalein retention is almost always found if varices have been formed.

Superficial erosions of the gastric mucosa are the next most frequent source of diagnostic error. Anatomically, the capillary network in the gastric mucosa is so rich and so profuse that the injection with India ink gives the mucosa a solid black appearance. Physiologically, these capillaries have a wide range of contraction and dilatation giving the mucosa at times a very pale or at other times a deep red suffused appearance. In this later stage, the most common lesion of the mucosa is hemorrhage which may occur without demonstrable ulceration of the mucosa. If this capillary oozing comes from a large enough area, it might be an immediate threat to life (5). This may be also part of the clinical picture found in hemorrhagic diseases such as thrombocytopenia or leukemia or in hepatic disease or bacteremias.

Cancer of the stomach is a rather uncommon cause of profuse gastric hemorrhage. If it occurs, it is usually late in the disease and is associated with loss of weight, mass in the epigastrium and characteristic X-Ray and gastroscopic findings and perhaps metastatic nodes in the supraclavicular fossa. Polyps and benign tumors are relatively rare but occasionally cause profuse hemhorrhage. The diagnosis again is clarified by X-Ray and gastroscopy. Hiatus hernia is an occasional cause of severe gastric hemorrhage, particularly in elderly people. Here the pain is aggravated by lying down and relieved by sitting or standing and the X-Ray picture is characteristic. There are some bleeding lesions of the lower gastro-intestinal tract which cause melena and must be differentiated. These are ulcerative colitis or enteritis, regional ileitis, ulceration in Meckel's diverticulum, carcinoma of the colon, amebiasis, tuberculous enteritis or colitis, typhoid, bacillary dysentery, cholera, etc. Here the symptoms of diarrhea, lower abdominal pain or obstruction, point to involvement of the caudad portions of the bowel. There are occasional rare causes such as subacute bacterial endocarditis with infected embolization which produce massive gastric bleeding.

## DIAGNOSTIC PROCEDURE

On admission, after emergency shock measures have been taken, blood should be obtained for red blood count, hemoglobin, hematocrit and typing. Stool and vomitus should be inspected for evidence of gross blood. Blood pressure readings should be taken and charted at very frequent intervals. A short time later platelet count, coagulation, bleeding and prothrombin time should be determined to rule out an intrinsic blood dyscrasia. Plasma protein, blood urea nitrogen, sodium and chloride and $CO_2$ combining power determination should also be obtained. Bromsulfalein and cephalin flocculation tests should be done to determine liver function.

The level of the blood urea nitrogen is very important. There has been some controversy as to the cause of azotemia in gastro-intestinal hemorrhage. It has been fairly well determined that these factors play a part: 1. Dehydration, shock and hemorrhage produce anoxemia, diminished renal blood flow and consequent renal impairment. 2. There is increased tissue catabolism. 3. There is increased absorption of digested blood protein.

Stevens (6) et al claim the last factor, i. e., digestion of blood protein, to be the most important. They demonstrated elevated blood urea nitrogen in normals fed blood by stomach tube. Gregory's (7) group demonstrated anoxemia of the kidney from shock and a longer persistence of the azotemia. Whatever the cause in such a single hemorrhage, the blood urea nitrogen reaches its maximum in about 24 hours and returns to normal in about three days. Continued elevation of blood urea nitrogen usually indicates continued hemorrhage. Incidentally, it might be mentioned that azotemia does not occur with bleeding into the colon. The degree of azotemia is a very valuable index to the severity of the bleeding and as a prognostic clue. If the blood urea nitrogen is below 30 mg%, the outcome is almost always favorable. One third of

the cases, when blood urea nitrogen rises above 50mg%, terminate fatally and two thirds of the cases with blood urea nitrogen above 70mg% die. An elevated blood urea nitrogen above 100mg% indicates pre-existing kidney disease.

X-Ray examination of the gastro-intestinal tract is essential and the question as to when it best be done is a matter of some controversy. In the past, it was the practice to wait two or three weeks, but this attitude has changed and the accepted procedure is to make the radiographic study as soon as the patient has completely recovered from shock. It is our belief that as soon as the patient is able to tolerate food or medication orally, he can tolerate a barium meal. Care should be taken to avoid abdominal manipulation during fluoroscopy. It is advantageous to study these cases early to detect some of the small ulcers which have a tendency to heal quickly. Even then, frequently no ulcer niche will be seen if the crater is filled with a thrombus. The Hampton technique is very valuable in demonstrating the duodenal cap in patients with hemorrhage. With the patient supine, he is rotated to the left and several swallows of barium are given. A film is then taken of the fundus area. The patient is rotated to the right and the lower portion of the stomach fills. The lesser curvature is then seen in relief. The cap is allowed to fill and the patient is rotated back supine and then to the left. Air and barium will fill the cap and it will be seen in double contrast. The second portion of the duodenum also will be seen. This procedure avoids the trauma of pressure and manipulation.

In instances of superficial erosion or gastritis, diagnosis by X-Ray is impossible and can be made only by gastroscopy. If no esophageal varices are visualized and there is no bromsulfalein retention, gastroscopy can safely be done on the second or third day.

## MANAGEMENT OF THE ACUTE STAGE

The management of ulcer hemorrhage requires sound clinical judgment and watchfulness. If the hemorrhage has been massive and the patient is in shock, the first consideration is restoration of blood volume.

Dripps and Comroe (8) have shown that tachycardia and fall in blood pressure are not invariable findings following hemorrhage. Compensatory mechanisms actuated by pressor receptors in the aortic arch and the carotid sinus area stimulate vasoconstrictor and cardiac centers with resulting increased peripheral resistance and cardiac activity. They have shown that this mechanism can compensate for losses of blood up to 1200 cc to 1500cc which they consider a critical level. If the loss of blood exceeds this, however, the compensatory mechanism breaks down and classical shock supervenes. Shenkin (9) and his group bled human volunteers from 500 to 1500cc and found no significant change in pulse rate as long as they remained supine. They divided the effects of hemorrhage in normal men into three stages of severity: 1. The subject is symptom-free and pulse rate and blood pressure are normal at rest. On arising there is acceleration of pulse rate and some diminution of blood pressure. 2. The subject is symptom-free while supine but on assuming an upright position, syncope develops. 3. Syncopal attacks occur even in the recumbent position.

Whole blood is by far the best replacement and should be obtained as soon as typing and cross-matching can be done. In the interim, plasma should be administered intravenously to prevent irreversible shock. All of our shock cases received 1 to 10 transfusions of 500cc of whole blood. The older concept of the danger of transfusion causing sudden rises in blood pressure is untenable. Blood has a favorable effect on shock patients and the blood pressure is usually abnormally low. The thrombocytic elements added by transfusion, also tend to favor clotting and thus decrease hemorrhage. The effect of early transfusion in bleeding ulcer has been adequately described by Kirsner and Palmer (10) and Browne and MacHardy (11).

With blood transfusions being given, the patient is watched hourly for evidence of lessening of shock. The pulse should get slower and the blood pressure rise to normal levels. The hemoglobin and hematocrit should cease to fall and the sweating and faintness should lessen. Frequently, if the patient seems symptomatically better, we use the tilting or foot-down position to check his clinical condition since many of these patients will fall into Shenkin's second group and have no sign of shock while supine but show evidence of it in the foot-down position. The determination of the blood volume by the Evans Blue method has been utilized but since this procedure is not accurate to a very high degree we have depended on clinical findings.

Parenteral fluids in addition to blood are also given. If there has been much vomiting, the chloride will be low and alkalosis may be present. These patients should receive normal saline or glucose in saline. If, in the presence of high blood urea nitrogen the sodium and chloride is elevated, glucose in distilled water should be given. The fluids are most conveniently given by slow intravenous drip, but recently, when we encountered difficulty in giving fluids intravenously the subcutaneous administration has been facilitated by the preliminary injection of 250 units of hyaluronidase. Sufficient fluid must be given to maintain a urinary output of 1000cc.

We have used buffered Thrombin in several cases. This substance, the use of which was originally described by Daly (12), is given in the following manner: In order to prevent inactivation of thrombin by gastric acidity, 30cc of seventh molar phosphate buffer with a pH of 7.6 is given. Five minutes later, another 30cc of this buffered solution in which is dissolved 10,000 units of thrombin is given. If necessary, this is repeated at 3 to 4 hour intervals. Daly found 17 of 21 patients responded to 1 to 3 doses. Where larger vessels are bleeding, thrombin cannot control the hemorrhage.

During the acute stage, the only medication necessary is sedation. We feel that the use of morphine, formerly the most widely used medication in the treatment of shock, is not physiological. It increases nausea and pylorospasm. Demerol[r] gives about as good sedation without the nausea and the lessened spasm. We have replaced morphine by Demerol[r] in all our bleeding ulcers. Barbiturates are also of value in decreasing apprehension and diminishing gastric motility and secretion. They may be administered subcutaneously or by rectal suppository. We do not

use antacids or other medication in the shock state. The question of feeding is also important. In the acute shock state, nothing can be tolerated by mouth. Formerly the patients were starved for long periods of time but we feel that as soon as nausea, vomiting and shock have been overcome the patient should be given oral feedings, milk in small amounts usually being the feeding of choice.

Some fifteen years ago Meulengracht advocated feeding of a full diet, pureed in form, to patients with bleeding ulcer. Since then, the technique of feeding rather than starvation of bleeding ulcers has been practically universally adopted. This was not new with Meulengracht. Even as early as 1901 Lenhartz advised six small feedings daily in ulcer hemorrhage. Andresen in 1927 again brought it to the forefront.

After the shock phase has passed, patients are put on small hourly feedings of milk, cream, protein hydrolysates and a little later cooked cereal, junket, custard, tapioca and cottage cheese. Pureed fruits are then added and gradually feedings spaced at longer intervals until six feedings per day are given. At this stage pureed meats, fish and vegetables can be given. If the night pain awakens the patient, he can be fed through the night. If this is particularly distressing in a duodenal ulcer, inserting a tube into the stomach through the nose and anchoring it carefully to prevent its passage into the bleeding area will allow the continuous drip of milk through the night as was advocated by Winkelstein.

At this stage of recovery it is advisable to give belladonna and phenobarbital four to five times daily as well as one of the antacids. If the patient is somewhat constipated we prefer using a mixture of aluminum hydroxide and magnesium trisilicate usually in the gel form, occasionally in the tablet form if the patient insists. If the stool is loose, plain aluminum hydroxide gel can be given. Even in the presence of rather marked hypochromic anemia we do not administer iron for a few weeks. In the first place, iron frequently increases gastro-intestinal irritability. It also has the disadvantage of rendering the stools black and masking possibly a subsequent occurrence of melena.

As the patient completely recovers from the effects of his hemorrhage, he is given the usual treatment for chronic peptic ulcer, i. e., bland diet, frequent feedings, belladonna and phenobarbital and one of the antacids—aluminum hydroxide or magnesium trisilicate.

## Results of Conservative Management

We have treated 68 patients with bleeding ulcer with the above regime. Of these, two died. One was a 60 year old man with an ulcer in the posterior wall eroding into the pancreatico-duodenal artery. He was in profound shock on admission and in spite of almost continuous transfusion he never rallied from his shock. Surgical consultants felt he never was in condition to operate. One other was a 58 year old male with severe hematemesis presumably due to ulcer hemorrhage. He was given 10 transfusions but shock continued unabated and he died on the fourth hospital day. No autopsy could be obtained.

The figures from this small series compare with larger series. Grier Miller and Kendall A. Elson (13) summarized statistics on 5,842 cases with a mortality of 8.3%. In their series, those cases treated surgically had a mortality of 28%. Of course only the most severe were operated upon.

## Indications of Surgery

With careful conservative management about 90% of patients can be successfully carried over the acute shock state and subsequent treatment done unhurriedly as an elective procedure. It is concerning the remaining 10% that discussion remains.

In recent years, surgeons have become more radical in their attitude to treatment during the acute bleeding stage. Dumphy & Hoerr (14) feel that a blood loss of 1500cc per day is critical and any more than this should be attacked surgically. Their technique is as follows: 500cc of blood is given every eight hours during the first day. If at the end of 24 hours the patient has not gained ground, with lessened shock and increased hemoglobin and hematocrit, laparotomy is done as soon as circulation is stabilized. If hemorrhage is of exsanguinating proportions, continuous massive transfusions are given.

The attitude toward types of operation is also changing. The older concept of cauterizing or ligating the vessel at the base of the ulcer or ligating the feeding vessel extraviscerally or local excision of the ulcer has been changing to the more radical and curative procedure of subtotal gastrectomy (15).

In this stage the surgical mortality is high, reported by various authors between 25 and 70%. When we consider, however, that without surgery these patients would almost certainly succumb, any procedure is worthwhile if it offers a chance of salvaging a life.

## Surgery After the Acute Hemorrhagic Episode Has Been Controlled

Once the acute bleeding has been controlled, the question of surgery as a prophylactic measure comes up. In this respect there are four factors to be taken into consideration: 1. The age of the patient. 2. The number of hemorrhagic episodes. 3. The ability to keep the ulcer under control. 4. The site of the ulcer.

In patients over 45 years of age, it is universally accepted that the occurrence of one severe hemorrhage is indictation for elective subtotal gastrectomy. The blood vessels of these patients have undergone a certain degree of sclerosis and they are not as flexible as those of younger patients. Subsequent hemorrhages at older ages would be too dangerous to risk and these patients should have subtotal gastrectomy as soon as all the effects of the hemorrhage have been overcome.

In the younger patients there is a certain amount of speculation. Many believe that if two previous hemorrhages have occurred, that operation should be done. Others state that the mortality of succeeding hemorrhages diminishes and conservatism is indicated. Our own feeling is that the other two above mentioned factors should aid in the decision.

Patients in whom it is difficult to control ulcer symptoms should be earlier candidates for surgery. These include men who cannot forego the use of alcohol or who cannot avoid dietary indiscretion, or in whom, because of the stress of emotional tension or physical exhaustion, symptoms continue. They are much more prone to have an erosion into a major vessel with recurrence of serious hemorrhage.

The site of the ulcer is of prime importance in arriving at a decision as to operation. Almost all fatal hemorrhages in duodenal ulcers occur with ulceration of the posterior wall with erosion into one of the major tributaries of the pancreatico-duodenal artery or at the lesser curvature of the stomach with ulceration into the left or right gastric artery. Should X-Ray examination reveal the ulcer in one of these sites, there is an additional factor in favor of early operation.

In a younger individual the presence of one or both of the last two indications would certainly influence us to urge surgery.

## SUMMARY

We have attempted to outline our management of cases of severe hemorrhage from peptic ulcer; to indicate various other causes of massive gastro-intestinal bleeding and to show how these cases can be evaluated during the acute shock stage.

We have also tried to point out the indication for surgery during the acute stages in an attempt at salvaging the lives of these severe cases who practically always go on to exsanguination.

Finally, we have discussed the management of these patients after the hemorrhage has been brought under control and stated the factors which influence our decision as to whether or not elective surgery should be recommended.

## CONCLUSIONS

1. Massive hemorrhage from a peptic ulcer is a dire emergency that requires continuous careful observation and treatment.

2. These patients require adequate transfusions of blood to replace blood volume and overcome shock.

3. About 90% of patients treated adequately but conservatively respond and hemorrhage is brought under control.

4. In the small remainder who do not respond in 24 hours, emergency surgery is indicated if these patients are to have any chance to survive.

5. The indications for elective surgery after control of the hemorrhage has been discussed.

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# CHRONIC PANCREATITIS WITH STEATORRHEA FOLLOWING MUMPS WITH ACUTE PANCREATITIS

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BOCKUS (6) states that "the occurrence of fatty diarrhoea following some cases of infectious parotitis has caused me to speculate concerning the possibility of permanent damage to the pancreas or intestinal lymphatic system in such cases. A casual review of the literature fails to throw any light on this relationship, since the presence or absence of mumps is not mentioned in the majority of the case reports dealing with chronic steatorrhea." In reviewing the literature on mumps pancreatitis we have found no mention of chronic steatorrhea following this complication.

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## CASE HISTORY

B.G. No. 48 8418, a sixty-year-old railway ticket agent, was well until April of 1946. At that time he developed bilateral parotitis and, within twenty-four hours, a left orchitis. Two members of his family were convalescing from mumps. His improvement was steady until the eighth day following the onset of his illness when he suddenly became profoundly weak, passed a large tarry stool, and fainted. More such stools were passed that day, and the following day (April 22, 1946) he was admitted to the Kingston General Hospital.

On that admission, he complained of weakness, fatigue, and moderately severe pain—described as a sense of pressure—in the epigastrium and to the left of the umbilicus. Functional enquiry disclosed no previous ill health, loss of weight, dyspepsia or abdominal pain. On examination, he was pale, temperature 99.4, pulse 80, blood pressure 130/70,

respirations 20. The abdomen was tender, this being most marked in the epigastrium. The left testicle was slightly swollen and tender. Haemoglobin was 10.6 grams %, R.B.C. 3.8 million per cu.mm. No definite diagnosis was made at this time. Between April 23, and May 21, 1946, he continued to complain of epigastric pain, severe enough to double him up, and at times required morphine. Small hematemeses occurred and tarry stools continud to be passed. He required repeated transfusions and by May 21, 1946, when there was no evidence bleeding had stopped, his haemoglobin had reached a level of 4 grams%. During this time, a low grade fever (to 100° F) persisted. It was decided that an exploratory laparotomy must be done, and this was carried out. The liver and spleen were normal, but unfortunately, no mention was made of the pancreas. The surgeon believed a papilloma could be felt in the prepyloric area, and a partial gastrectomy was done. The gross specimen was not remarkable, and no papilloma was present. Microscopically, the stomach and first 3 cms. of the duodenum showed patchy shedding of the surface epithelium, and the stroma was infiltrated with cells of mononuclear type. These changes were most marked in the duodenum. The submucosa and muscular layers were normal. Postoperatively, bleeding continued to a lesser extent, and the patient was discharged June 8, 1946, with a haemoglobin of 6.8 grams%.

Between 1946 and the spring of 1948, he was under observation by the surgical service. He complained of some flatulence, urgency and frequency of defaecation, but this was not investigated. In the spring of 1948, he complained to his family physician that he was unable to see in the dark. It was then recognized that from July of 1946 he had been having three to five light, bulky stools, accompanied by copious amounts of "oil." The family physician prescribed Pancreatic Extract, 6 grams daily. This resulted in the disappearance of "oil" from his stools, but he continued to have three to five light colored movements daily. He was then admitted to hospital.

On admission (September 26 1948) he complained of generalized weakness, flatulence, frequency of bowel movements, and night blindness. He was 20 pounds below his usual weight. The tongue was smooth and reddened and the skin showed the typical features of Vitamin A deficiency. The abdomen was slightly protuberant and felt "doughy." Laboratory investigation revealed a normal urine, haemoglobin 10.6 grams%, R.B.C. 3.37 million per cu.mm., W.B.C. 4,800 per cu.mm. with lymphocytes 36%, neutrophiles 60%, bands 1% eosinophils 1%, monocytes 1%, and basophils 1%. Sedimentation rate (Westergren)—6mm. in the first hour. Blood Urea—35mgm.%. An oral glucose tolerance test gave the following results: fasting—72mgms.%; 30mins.—85mgms.%; 60 mins.—90mgm.%; 120 mins.—93mgm.%. Plasma Alkaline Phosphatase—35 King Armstrong units. A Histamine Test Meal revealed no free hydrochloric acid. Plasma proteins—total 6.4 gms.% with albumin 4.66 gms.% and globulin 1.74 gms.%. The plasma prothrombin content was 35% of normal. Twenty-four hours after parenteral administration of 1 mgm. of synthetic vitamin K, this rose to 75%. Radiography after barium meal showed slow emptying of the stomach, but rapid movement through the small intestine. The latter showed barium scattered throughout, with gross segmentation, and complete loss of the normal mucosal pattern. Barium enema revealed a greatly dilated large bowel, again with barium adherent to the wall throughout, and loss of mucosal pattern.

A diagnosis of chronic pancreatitis with pancreatogenous steatorrhea following mumps was made, and he was discharged on a diet containing 30 grams of fat, 20 grams of Pancreatic Extract U. S. P. daily, and intensive vitamin therapy by mouth. He was given daily, in divided doses, Vitamin A 40,000 units, Vitamin D 2000 units, ascorbic acid 450 mgms., thiamine hydrochloride 18mgms., riboflavin 18mgms., nicotinamide 90 mgms., menadione 30mgms., pyridoxine 3mgms., and pantothenic acid 30mgms. Eight days later he returned, greatly pleased. He was having one normal bowel movement daily, his night vision was improving rapidly and he had gained 4 pounds. His vitamin medication was reduced so that he received in a supplement approximately five times the accepted daily adult requirements. The low fat diet was continued and the dose of pancreatic extract was reduced to 15 grams a day. Subsequently the dose of pancreatic extract was further reduced, and a dosage below 10 grams daily was found to result in an increase in the number of stools.

Nine months after treatment was began he was re-admitted to hospital for follow-up study. He had been carrying along satisfactorily at his work but found that he tired easily. A new complaint was that he was occasionally constipated and as a rule he had one bowel movement a day of normal color and volume. An attack of influenza caused diarrhoea which was controlled by a temporary increase in the dosage of pancreatic extract. He was free of all signs of vitamin deficiency and abdominal examination was negative. Laboratory investigation revealed a normal urine, haemoglobin 11.0 grams %, R.B.C. 3,500,000 per cu. mm., W.B.C. 3,000 per cu. mm. with lymphocytes 44%, neutrophiles 44%, bands 2%, basophiles 1% and monocytes 9%. Sedimentation Rate 8 mm. in the first hour (Westergren). An oral glucose tolerance test gave the following results: fasting—76 mgm.%; 60 mins.—106 mgms.%; 90 mins.—115 mgms.%; 120 mins.—93mgms.%.

The urine collected at the time of the last two specimens showed traces of sugar. A Histamine Test Meal showed 39 and 65 clinical units of free acid in the last two specimens collected. The plasma prothrombin content was 71% of normal. Plasma proteins—6.3 gms.% with albumin 4.5 gms.% and globulin 1.8gms.%. Serum alkaline phosphatase 21 King Armstrong units. Serum Cholesterol 177 mgms.%.

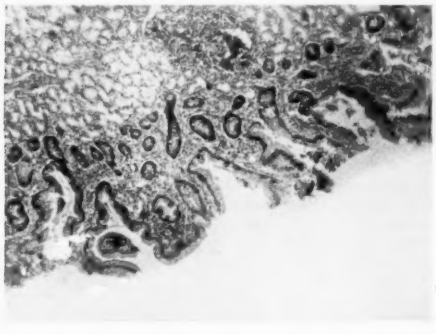

Fig. 1. Section through the mucosa of the pyloric antrum.

Fig. 2. Distribution of barium 2 hours after barium meal.

Radiography after barium meal showed considerable improvement in the small bowel pattern, though passage through the bowel was rapid and the head of the meal was in the caecum in one hour. Barium enema showed a large bowel of smaller diameter than previously though still greater than average.

## DISCUSSION

The first adequate description of acute pancreatitis in the course of mumps is that of Cuche (7) in 1897. Textbooks of medicine and infectious diseases, as well as case reports, place the incidence of this complication between 1.5% and 15% (1,2,3). The clinical picture (2,4,5,9) agreed on by many authors consists of the onset, usually between the third and ninth days (1) of the disease, of epigastric or hypochondrial pain, nausea, vomiting, fever and malaise. Tenderness is usually most marked in the epigastrium. Melena, glycosuria and steatorrhea (13) may or may not be present during the acute phase. Usually, the duration of abdominal symptoms is under one week, and recovery is uneventful. Apparently, as in Farnam's case (11), severe pancreatitis can occur without any detectable disturbance of internal or external pancreatic function, and no sequelae. The case of Merklen and Gounelle (12) had recurrences of pain for four and one-half months. In none of the case reports in the literature did we find described chronic steatorrhea following the acute pancreatitis, nor did we find any description of the pathological features of the pancreas in the chronic state. Good descriptions of the acute changes are available in the two cases of death during mumps pancreatitis reported by Lemoine and Lapasset (8) and by Sabrazes, Broustet and Beaudiment (10).

## SUMMARY

1. A case of chronic steatorrhea following mumps with acute pancreatitis is reported.

2. A brief discussion of acute mumps pancreatitis and its usual clinical course is presented.

3. Attention is drawn to the paucity of clinical and pathological data available regarding chronic pancreatic dysfunction following acute mumps pancreatitis.

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# THE CLINICAL DIAGNOSIS OF JAUNDICE

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THE PATHOGENESIS of jaundice is a fascinating study in pathologic physiology. The pathologist, after post-mortem examination, is quite capable of giving a detailed explanation of the physiologic mechanism involved. Unfortunately such lucidity is denied the clinician. He is confronted by a jaundiced patient and a handful of equivocal laboratory reports but his evaluation of the disease, while lacking the scientific preciseness of the pathologist, nevertheless, achieves a degree of accuracy directly proportional to his diagnostic acumen. To achieve an acceptable percentage of success in the diagnosis of jaundice the clinician must recognize his limitations as well as his abilities. Furthermore, he must not be lured into the common error of attempting to make a pathologic diagnosis. In this communication we shall attempt to describe a diagnostic routine for the study of jaundiced patients.

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The classification of jaundice is still subject to individual interpretation. For general use that of Rich has stood the test of time. Ivy and others have suggested that the only practical way to study a jaundiced patient is from a treatment point of view. This is very logical since the clinician must decide as soon as possible whether the jaundice is "medical" or "surgical." The longer he defers his diagnosis the more difficult it will become because of increasing hepatocellular damage. However, it is not always immediately possible to identify a case of jaundice as being "medical" or "surgical." It is necessary, therefore, to add a third

group: those that will require a period of observation before the final diagnosis is established. In order to set a limit on the time available for observation one is justified in allowing one to three weeks. It may easily take as long as two weeks to differentiate hepatocellular from obstructive jaundice. On the other hand, if a clinical diagnosis has not been made after three weeks, further study is potentially more dangerous than informative. If a diagnosis cannot be established within this period of time exploratory surgery is justified.

In arriving at a diagnosis for a jaundiced patient the clinician must first decide whether it is hemolytic, hepatic, obstructive or mixed in origin. He then decides whether it is "medical" or "surgical." Hemolytic and hepatic jaundice are "medical," obstructive and mixed jaundice are "surgical." To arrive at these conclusions quickly it is necessary to follow a certain routine so as to conserve time and effort.

### OBSERVATION OF THE FECES

The single most important test in the study of the jaundiced patient is the daily observation of the stool by the attending physician. This is also the most difficult to obtain. The average examiner observes the stool with a reluctance that is second only to his desire to avoid doing a rectal examination. Nevertheless, a careful and intelligent observation of the jaundiced patient's stool may be all the laboratory procedure necessary to establish a clinical diagnosis with sufficient accuracy to clarify the indication for treatment. Because of the importance of observation of the stool it is well to review certain aspects of it. First of all, it is a procedure which cannot be delegated. The physician himself must observe the stool because reports of color are usually unreliable. The true, acholic stool is no shade of yellow or brown; rather, it is white or slate-grey. The term "clay-colored" is probably one of the most misused of medical cliches and is practically without meaning. The term probably originally referred to potter's clay. This is a commodity with which the average American citizen is totally unfamiliar and, therefore, in no position to use as a standard. We have heard acholic stools described by the patient as being "like tooth paste." To be scientifically accurate it would be well to know what brand is referred to but, in general, it seems to convey more to the patient than the term "clay-colored." It is, of course, important not to give bile preparations by the mouth during the time the stool is being observed. If the stool is persistently or intermittently acholic the patient is usually a candidate for exploratory surgery. If the stool is persistently yellow or brown it usually indicates "medical" jaundice. If the stool is acholic, the jaundice recent and evidence of hepatocellular damage is found, a period of observation and supportive therapy is indicated prior to final diagnosis and/or exploratory surgery.

### HISTORY

The history of a jaundiced patient is of unusual interest but it must be directed toward certain definite goals. The past and personal history attempts to discover hereditary, toxic or traumatic factors. Similar disease in other members of the family is significant. The occupation may suggest the possibility of exposure to hepatotoxic chemicals or infections (sewer work). Associated illness (arthritis, rheumatism) may suggest the use of toxic drugs (cinchophen) or transfusions (virus hepatitis). Recent abdominal surgery may suggest trauma to the extra-hepatic duct system.

The story of the present illness is likewise important. A sudden onset with pain, chills and fever will usually indicate obstruction by calculi. If jaundice is the only complaint the picture is not as clear. Black or bloody stool and weight loss may indicate a malignant condition. It is well to remember that the patient's evaluation of his jaundice is unreliable. Often the patient is unaware of his jaundice until the comment of his associates directs attention to it.

### PHYSICAL EXAMINATION

Great care should be directed to the examination of the abdomen after a routine examination is completed. A palpable gallbladder in a soft belly is almost diagnostic of malignant obstruction of the extra-hepatic bile ducts. Muscle guard and signs of peritoneal irritation in the right upper quadrant suggest an inflammatory process (usually associated with calculi). Ascites suggests malignancy or cirrhosis. The color of the skin supplies a hint to the duration of the jaundice. A light yellow color implies recent and mild jaundice. An orange color suggests a deeper jaundice of longer duration. A greenish cast indicates a deep icterus which has been present long enough to be associated with some hepatic dysfunction. These colors are not diagnostic but are helpful in that yellow jaundice is usually seen in the hemolytic types and the green type in malignant obstructions.

### LABORATORY TESTS

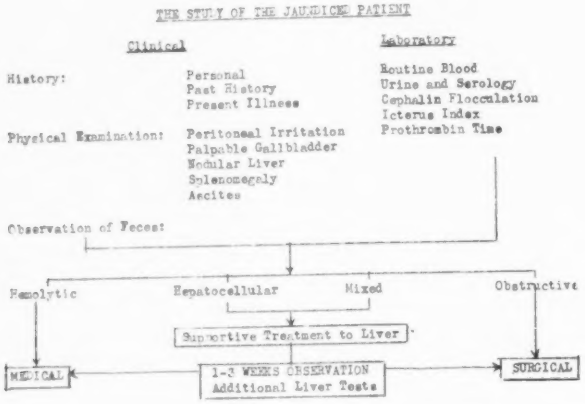
The clinical laboratory can supply indispensable information but it cannot supply a diagnosis. The determination of which tests are most useful will remain an individual decision. It will be conditioned by the clinician's experience with the interpretation of the various tests, the capability of the laboratory and the ability of the nursing staff to co-operate in the collection of specimens. In selecting tests for routine use we have limited ourselves in this manner. We attempt to select those procedures which will give the greatest amount of information with the greatest conservation of energy by the laboratory and nursing staffs. The procedures we have selected are the following:

1. Red and white cell count, hemoglobin and differential count.
2. Chemical and microscopic urinalysis.
3. Wassermann and Kahn.
4. Icterus Index—daily to establish a base line.
5. Cephalin Flocculation—to screen for hepatitis. If reported one or two plus, repeat and use Thymol Turbidity test for confirmation.
6. Prothrombin Time—use as a guide for Vitamin K dosage and as an index of impaired function if no response is produced by the administration of the vitamin.

These tests are simple to do, they add nothing to the nursing problem and little to the burden on the laboratory. In the majority of cases the information derived from the history, physical examination, observation of the stool and the above laboratory procedures will suffice to make a clinical diagnosis. Additional confirma-

tory tests include thymol turbidity to confirm the cephalin flocculation, hippuric acid test to measure the detoxifying potential and galactose tolerance to measure carbohydrate metabolism. If the clinician finds it difficult to be certain of the color of the stool, similar information can be derived from a quantitative determination of urobilinogen in the feces or urine. These tests, however, add a considerable burden to both the laboratory and nursing staffs.

The program for the study of a jaundiced patient can be outlined as follows:




## DISCUSSION

The differential diagnosis of jaundice is not a difficult procedure when the patient presents a classical or text-book picture of a disease entity. Two examples may be mentioned: those cases that develop jaundice associated with an acute right upper abdominal episode and those that develop jaundice late in the course of cirrhosis of the liver. Often, however, the jaundiced patient presents a picture which does not readily fall into an established clinical symptom-complex. It is essential for the clinician to appreciate that in such cases the establishment of a pathologic diagnosis at the bed-side is often impossible. He must, furthermore, realize that jaundice, while in no sense an emergency problem, requires prompt and specific treatment as soon as possible to minimize the hepatocellular damage which is present to a variable degree in all types. It is necessary, therefore, to start supportive therapy to the liver simultaneously with the diagnostic routine.

Therapy directed to support the liver will not confuse the diagnostic procedures and will actually fit well into a preoperative preparation plan. Supportive liver therapy consists of a high caloric, high protein diet supplemented with an oral intake of multivitamin pills and between meal feedings of a protein supplement. Protein intake may be further increased by the intravenous administration of an amino acid solution. The administration of oral bile preparations and vitamin K may confuse the diagnostic procedures and should be deferred until a diagnosis is made. An exception may be made in the case of vitamin K if it is to be used as a diagnostic test for liver damage.

The use of an unselected and lengthy series of laboratory tests is to be deprecated. Many tests devised for the diagnosis of jaundice are repetitious and most are non-specific. The two most useful procedures, in our experience, have been the cephalin flocculation test and the observation of the stool. The former acts as a screening test for active hepatitis and due to its unusual sensitivity will pick up most such cases. Personal observation of the stool by the attending physician is a remarkably accurate screening test for post-hepatic obstruction. These two screening procedures will, in themselves, indicate in most cases whether the jaundice is medical or surgical—assuming, of course, that an adequate history and physical examination have been done. If the condition is clinically undiagnosable exploratory surgery is indicated after a sufficient period of supportive therapy has been given. Exploratory surgery is perferable to such lesser procedures as peritoneoscopy or punch biopsy. The latter may actually be dangerous in the presence of obstructive jaundice. We have recently reported the occurrence of a biliary fistula and bile peritonitis following such a procedure. Although this may happen but rarely it would seem to be too grave a complication to take lightly. In summation one can say that the differential diagnosis of jaundice is essentially a clinical problem in which the laboratory can only give assistance. The final clinical diagnosis is necessarily a product of the clinician's diagnostic acumen and experience. There are no easy short-cuts.

## CASE REPORTS

The following selected case reports illustrate examples of jaundice which were difficult or impossible to accurately diagnose without laparotomy. An operation in each instance revealed the true nature of the condition and resulted in relief of symptoms.

*Case No. 1 R. T.* . . This 61 year old, white, male veteran was admitted to the hospital because of jaundice of one week's duration. It was noted from his records that he had been diagnosed as dementia praecox, hebephrenic type, had been declared incompetent and was under the care of a guardian. He was found to be quite obviously in a state of remission and had no serious disability from his psychosis.

Essentially the story of his present illness was as follows: He was well until the week previous to admission when he suddenly developed nausea and vomiting associated with a slight discomfort in the right upper quadrant. He also complained of shortness of breath. The pain did not bother him

much and his main difficulty was associated with the dyspnea and vomiting. He became weak and had to go to bed. About this time he was told that he was jaundiced, although the exact onset of the jaundice was difficult to determine. At the time of interview the patient was deeply jaundiced and yet was completely unaware of it.

Physical examination revealed a large, well developed, well nourished, white male of the stated age. He was pleasant, cooperative and ambulant. Except for his deep jaundice he did not appear to be ill. The pulse and temperature were normal. The head and neck were not remarkable with the exception of an icteric discoloration of the conjunctivae and mucous membranes. The chest was within normal limits and the lung fields were clear with the exception of an area of diminished auscultatory findings in the left base. No pathology could be diagnosed in the lungs. The heart was within normal limits and the blood pressure was 162/84. The abdomen was large and somewhat protuberant. The liver edge was palpable 4 cm. below the right costal margin and extended across the midline. There was some tenderness over it. An old, supra-pubic scar, which was well healed and asymptomic, was found. The genitalia were normal adult male. There was no evidence of edema and neurological examination was negative. The preliminary diagnosis was obstructive jaundice of unknown etiology, possible common duct stone; metastatic tumor of the liver to be ruled out.

A survey of his old records at the hospital revealed that he was previously admitted ten years before for the treatment of an acute urinary retention. At that time he was treated with a supra-pubic cystotomy to relieve urinary retention and later a transurethral resection of the prostate gland was done. The discharge diagnosis at that time was adenocarcinoma of the prostate. Because of the possibility of metastatic malignancy, these slides were obtained from the file and re-examined by the pathologist. The diagnosis on re-examination was: Adenocarcinoma of the prostate, Grade I.

He was seen in consultation with the surgeons and it was suggested that a urological examination be completed and the patient be considered for laparotomy within a week if a diagnosis could not be established. Urological examination revealed a hypertrophy of the prostate gland and trabeculation of the bladder. A tentative diagnosis of carcinoma of the prostate was made and transurethral resection and stilbestrol recommended. A note was made that metastatic involvement of the liver was unlikely since no evidence of bony metastasis in the pelvis was found on x-ray. A liver biopsy was obtained with the Turkel needle and the diagnosis was: "Liver tissue, showing extensive degeneration with many canaliculi occluded with inspissated bile, probably due to obstruction." During the period of observation his stool was found to be consistently gray in color.

The laboratory work revealed a red count of 4.8 million, a white count of 14.6 thousand which rapidly fell to 5.0 thousand and over 85% hemoglobin. Urinalysis was negative except for the presence of pyuria, which was in keeping with his prostatism. The Van den Bergh test was diphasic and the cephalin flocculation test varied from three plus to four plus. The icterus index varied between 30 and 92.

He was transferred to the Surgical Service and after the necessary preoperative preparation was subjected to laparotomy. At operation a large liver with a rounded edge was discovered and the gallbladder was found to be surrounded with numerous inflammatory adhesions. A large calculus was found impacted to the common duct and was removed without difficulty. A T-tube was placed into the common duct. The gallbladder was removed and the patient was returned to the Ward in good condition. His postoperative course was completely uneventful. The jaundice cleared rapidly and on the fifth postoperative day a cholangiogram revealed patency of the common duct with some dilatation of the ductal system. Intermittent clamping of the T-tube was started and he was sent home on a two week convalescent pass. He returned from this in good condition and after the cholangiogram was repeated and found normal, the T-tube was removed. He was discharged, at which time he was no longer jaundiced. Final treatment of his prostatic lesion was deferred to a later date. He was seen again three weeks after discharge and three months after operation at which time he was in good health.

Comment: This case represents a diagnostic problem which involved the differential diagnosis of metastatic hepatomegaly and common duct stone in a psychotic. The question of metastatic involvement of the liver could not be definitely ruled out by clinical examination alone. The marked precipitation in the cephalin flocculation test suggested hepatitis, which could be secondary to either a calculus or a metastatic malignancy. Since the stool was consistently acholic, exploratory laparotomy was indicated not only to establish the diagnosis but also to not overlook any therapeutic possibilities. Discovery of a common duct stone resulted in a favorable outcome.

*Case No. 2 H. A. G.* . . . This 61 year old veteran was admitted to the hospital for the treatment of chronic heart disease. The admitting doctor noted that the patient was jaundiced, acutely ill and drowsy. The heart was grossly enlarged and there was a mass in the epigastrium. The impression of the admitting physician was cardiac failure associated with possible cirrhosis or hepatic carcinoma. The history revealed that the patient had a cholecystectomy and appendectomy in 1946. He recovered from the operation satisfactorily and was well until about a year ago when he developed dyspnea on exertion which became progressively worse and finally required digitalization. This treatment was obtained from his private physician. He got along fairly well with his heart disease but about one week prior to admission he developed vague abdominal pain and became jaundiced.

Physical examination revealed a well developed, well nourished, white male of the stated age who was jaundiced and acutely ill. The head and neck were essentially normal although a deep icteric tint was noted in the conjunctiva and mucous membranes. Fundoscopic examination revealed evidence of arteriosclerosis. Basal rales were present in the lungs but otherwise they were within normal limits. Examination of the heart revealed the apex beat to be to the left of the midclavicular line. A systolic murmur was present but was not transmitted to any other area. The blood pressure was 158/88 and the pulse was 72 with auricular fibrillation present. The edge of the liver was palpable three fingers below the right costal margin. In the epigastrium a smooth non-tender mass, about 10 cm. in diameter, was found. This appeared to represent the left lobe of the liver. The remainder of the examination was non-contributory and the impression was: arteriosclerotic heart disease with mild decompensation and hepatomegaly of unknown origin, to be studied further.

Laboratory Examinations: On admission the cephalin flocculation test was 2 plus, icterus index 31, cholesterol esters 106, serum bilirubin 4.6 and Van den Bergh delayed direct. The Van den Bergh remained direct and the icterus index remained about 30. The serum bilirubin fell to 1.9 and varied from about one to two. After two weeks the cephalin flocculation became 3 plus, the alkaline phosphatase 15.1 and thymol turbidity 9 units. The stool at this time was negative for blood and brown in color. On admission the NPN was 35.7, the total protein was 8 with a reversal of the albumen-globulin ratio, albumen 3.31, globulin 4.69. The copper sulphate test revealed a specific gravity of 1.060, hemoglobin 17.8 and cell pack of 38 mm. The serology was negative. The blood count was within normal limits and the urinalysis was negative. X-ray examination on admission revealed a general cardiac enlargement and congestion of the pulmonary trunks. A barium enema was normal. A flat plate of the gallbladder region showed no calculus and a GI series was negative.

The patient was admitted on the Medical Service and was treated for cardiac decompensation. The treatment was very successful and after evidence of cardiac failure had subsided he was transferred to the Surgical Service. After preoperative preparation and approximately four weeks after admission to the hospital, he was subjected to a celiotomy.

A transverse incision was made in the right hypochondrium and the abdomen was opened, revealed many adhesions in the right upper quadrant, the result of the previous cholecystectomy. Exploration revealed that the epigastric mass was an enormously enlarged left lobe of the liver. The common duct was found to be thick walled and dilated approximately to 2 cm. in diameter. No calculi could be palpated in the common duct. The duodenum was, therefore, mobilized by rotating it medially in order to palpate the head of the pancreas. In so doing a duodenal diverticulum was exposed, lying in the angle between the duodenum and the common duct. The common duct was opened and a probe passed upward into the liver, without meeting an obstruction. It was possible to insert the probe in two directions, probing both the right and left hepatic ducts. The probe could not be passed distally into the duodenum, as it seemed to catch on a fold of mucosa. It was felt that a transduodenal exploration of the ampulla of Vater was indicated to rule out possible obstruction at

this level. The duodenum was, therefore, opened longitudinally in its second portion and on its anterior surface. The ampulla of Vater was demonstrated and found to be normal and to contain an adequate stoma. A probe was readily passed upward through the ampulla into the common duct. A long Cattel type of T-tube was then brought through the choledochostomy and out into the duodenum so that approximately three cm. of it projected out of the ampulla of Vater into the duodenum, thereby insuring adequate biliary drainage. The choledochostomy incision was closed with interrupted #00 chronic catgut sutures. The duodenal diverticulum was amputated and the two defects in the duodenum were closed transversely with a double row of continuous chromic catgut sutures and an interrupted row of intestinal cotton. The operation was terminated and the patient was returned to the Ward in good condition.

The postoperative course was uneventful with the exception of some bradycardia. He was permitted to go home on pass, still wearing his choledochostomy tube. He returned from pass six weeks later when, after cholangiography, the T-tube was removed and he was discharged.

Comment: This case represents the development of jaundice in a patient suffering with chronic cardiac decompensation. The cardiac decompensation was relieved without influencing the course of the hepatic disease. The cephalin flocculation test suggested increasing hepatic damage although the color of the stool did not indicate complete extra-hepatic obstruction. Because of the lack of clinical findings sufficient to make an etiologic diagnosis of the jaundice a laparotomy was elected. At operation the cause of the jaundice became obvious and since it was a benign condition it was easily remedied. Complete recovery followed.

*Case No. 3 T.B.* . . . This 48 year old, white, male veteran was admitted to the hospital for treatment of jaundice, probably due to infectious hepatitis. His chief complaint on admission was lack of appetite and a loss of 40 pounds of weight in the past two years. He also had epigastric discomfort associated with bloating and belching. Approximately four weeks prior to admission he had an attack of diarrhea which lasted for three to four days and then disappeared spontaneously. Two weeks later he developed an attack of sudden severe pain which radiated to the right costovertebral angle. He had chills with this attack but although he took his temperature he could find no fever. One week later (about one week prior to admission) he first noticed greyish stools which have persisted to date.

Physical examination revealed an acutely ill, deeply jaundiced, white male of hyposthenic habitus. He appeared emaciated and older than the stated age of 48. With the exception of an icteric tint in the sclerae and mucous membranes, the head and neck were within normal limits. The chest was long and thin but the movements were normal and no adventitious sounds were audible. The heart was well within normal limits. The abdomen was soft and the solid organs were not palpable. There was no muscular rigidity or other evidence of peritoneal irritation. However, on deep palpation there was pain in the right upper quadrant. The remainder of the physical examination was of no pathological significance. The diagnosis at this time was obstructive jaundice, probably due to carcinoma of the head of the pancreas.

Laboratory work revealed a normal blood count, an icterus index of 43, a three plus cephalin flocculation and a prothrombin time of 48 seconds as compared to a control of 14. Repeated examinations of the stools were negative for blood and parasites. The serology was negative and the serum amylase was 16 units. The A/G ratio was albumen 3.55 units and globulin 4.15 units. The icterus index was repeated and found to be 63.

Because of the abnormal A/G ratio and positive cephalin flocculation test intensive supportive therapy to the liver was started in anticipation of a celiotomy and probably major surgery. However, about twelve days following admission he suddenly developed chills and fever, the temperature going over 102°. It was felt that a cholangitis could explain his entire picture and accordingly he was subjected to a celiotomy.

At operation the liver was found to be low lying and to have a thin sharp edge. The serosa of the anterior surface of the liver was covered with a reticular fibrosis. The gall bladder was contracted and practically empty of bile. The common duct was slightly dilated but not significantly so. However on the anterior surface of the common duct the same type of reticular fibrosis was present that had been noted in the liver capsule. The common duct was opened and explored discovering that it was possible to pass a probe through the ampulla of Vater with no difficulty. Passing a probe upward into the hepatic branches, however, met with resistance. It was possible to pass the probe beyond the obstruction in the left hepatic duct but it could not be passed more than 2cm. up the right hepatic duct. Throughout this procedure it was noted that the extra-hepatic biliary tract was practically devoid of bile. Even after probing both hepatic ducts no clear yellow bile was found. The only bile evacuated was a thick greenish bile which was being extruded from the gallbladder. A T-tube was sutured into the common duct and a specimen of the bile was sent for smear and culture. An appendectomy and liver biopsy were done and the operation was terminated.

The patient's immediate postoperative condition was good and he had an uneventful convalescence. However, the day after surgery less than 5 cc. of bile was excreted through the T-tube. The excretion of bile, however, gradually increased until the fifth postoperative day when he was draining normal amounts. Culture of the bile revealed hemolytic staphylococcus albus. A cholangiogram during the postoperative period revealed a demonstrable narrowing of the intra-hepatic biliary radicles. He was permitted to wear the T-tube for three months after which another cholangiogram was done and since no obstruction was apparent it was removed. A follow-up a year later revealed him to be in good health with no complaints.

Microscopic examination of the liver biopsy revealed numerous small areas of focal necrosis throughout the entire liver parenchyma. These necrotic areas were scattered through all the hepatic zones, having no relation with either the central vein or the periportal spaces. The liver cells adjacent to these necrotic areas showed various stages of degeneration and regeneration. In all portions of the lobules, Kupffer cells could be seen which were filled with a dark greenish-brown pigment which was believed to be bile. The hepatic ducts were not dilated as in an obstructive jaundice. The pathological diagnosis was hepatitis, acute, cause undetermined but probably due to an ascending infection.

Comment: This case represents a severe hepatitis, secondary to a chronic cholangitis. Although acute liver damage was present, as indicated by the biopsy, recovery was rapid and complete once a specific diagnosis was made and specific treatment (decompression of the extra-hepatic biliary tract and antibiotics) was instituted.

*Case No. 4 C. P.* . . . This 29 year old, white, male farmer was admitted to the hospital because of undiagnosed, chronic jaundice of nine months duration. There was a marked pruritus associated with the jaundice. His appetite was poor and there was a feeling of malaise which had become progressively more severe. He had lost thirty pounds in the past six months. The stools were brown in color. There had never been any intolerance to fatty foods and there had been no jaundice in any of his immediate family. This was the first attack of jaundice he had ever had.

Physical examination revealed an ambulant, well developed and well nourished white male of the stated age. The skin was an olive green color and showed numerous scratch marks. The head and neck were essentially normal with the exception of a deep yellow color to the sclera. The chest was entirely within normal limits and the lungs were clear and resonant. The heart was normal in size with regular and normal sounds. The abdomen was soft with slight tenderness in the right upper quadrant where the liver was palpable 4 cm. below the costal margin. Rectal examination was not remarkable. The initial impression was obstructive jaundice of undetermined type.

Routine blood, urine and serology were within normal limits. The icterus index was about 40 and the cephalin flocculation test was 2 plus. The Van den Bergh test gave a delayed direct reaction. The alkaline serum phosphatase was 15 King Armstrong Units. The blood cholesterol was 354 mgm. %. Tests of the stool for parasites were negative. The patient was observed for a period of nine months during which time every conceivable test for jaundice was run without adding materially to the picture described above. The serum alkaline phosphatase did rise toward the end of this lengthy period of observation, going over 35 units. The albumen-globulin ratio gradually fell and the cephalin floc-

culation test reached 4 plus. These findings, of course, reflected the increasing liver damage.

X-ray examinations were not contributory. A questionable lesion in the duodenum could not be definitely established by G. I. series.

Approximately nine months after he was first seen the patient was subjected to laparotomy, at which time a primary carcinoma of the common duct was discovered associated with a benign adenoma of the right hepatic duct. The benign adenoma was excised and the carcinoma of the common duct was removed by segmental resection and end to end anastomosis of the common duct. The postoperative course was uneventful with the exception of several bouts of cholangitis which responded promptly to streptomycin. Six months after operation the patient was well, ambulant and his jaundice had subsided.

Comment: This case is presented as an example of prolonged observation. Despite a nine month period of observation and the use of every conceivable type of test a diagnosis could not be established without laparotomy. At laparotomy the pathology was evident and specific treatment resulted in a rapid relief of symptoms. There is no question that the prolonged period of observation definitely hindered this man's possibility of achieving a complete recovery: first, because of the increasing liver damage and secondly, because the possibility of metastasis from the malignancy was enhanced.

SUMMARY

1. The differential diagnosis of jaundice is discussed from a clinical point of view. The necessity for arriving at an early definitive treatment schedule is emphasized.

2. The importance of using a few, well selected, laboratory procedures is indicated. The significance of careful examination of the stool is stressed.

3. A series of case reports is included which illustrates the necessity of exploratory laparotomy to establish the diagnosis in difficult cases.

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# ABSTRACTS ON NUTRITION

BRUCH, H.: *Physiological and psychological interrelationships in diabetes in children.* Psychosomatic Med. 1949, XI, 4, 200-210.

Psychiatric study of 37 diabetic children was made, and compared with a study of purely obese children. In childhood obesity, common mental characteristics could be easily recognized and they were found to be related quite definitely to the evolution of the obesity. "One might say that obesity *is* a way of life, and though resented as an embarrassing handicap, serves the function of giving the security of size." In diabetic children, no mental factor of such central importance was recognized in a comparable study. Diabetes enforces a certain way of life to which the child and his family will react according to pre-existing but unspecified patterns. Diabetes seems to reinforce existing problems.

GROTTS, B. F. AND ARNOLD, J. H.: *Functional hypoglycemia in children.* Arch. Pediat. 1949, 66, 10, 462-475.

The cases of two children with functional hypoglycemia are described. The condition is uncommon in children. All reported cases have had repeated isolated episodes of hypoglycemia interspersed with periods of complete remission. The cause seems to be a lack of storage of liver glycogen and/or some fault in the nervous or endocrine carbohydrate regulatory mechanism. Immediate exciting causes for the attacks are sometimes decreased food intake or unusual energy expenditure. Immediate relief is obtained by giving glucose. A satisfactory prophylactic treatment consists in a high protein diet, low carbohydrate diet, and the avoidance of fasting and over-exertion. The diagnosis rests on the combination of history, physical examination, laboratory tests and the response to dietary management.

GUTIERREZ, P. D. AND FERNANDEZ, M. C.: *The modern role of vitamin $D_2$ in cutaneous tuberculosis.* (Acta Med. Philippina, Jan.-March 1949, Vol. V, No. 3, 17-23).

The authors are obtaining excellent results in 3 cases of lupus vulgaris and 2 cases of scrofuloderma in the University of the Philippines. Squibb's vitamin $D_2$ capsules containing 50,000 units per capsule, were used in the cases. Four capsules are given daily for 2 weeks followed by a 2 week rest period, after which administration is resumed. It is a two-weeks-on, two-weeks-off regime. For children, the daily dose is 3 capsules. Sufficient milk is taken daily to ensure adequate calcium intake. All cases have shown remarkable initial and progressive improvement thus far (2 months). Vitamin $D_2$ and calciferol are identical. Calciferol is obtained from natural ergosterol by getting rid of lumisterol and purification of tachysterol. Contraindications to calciferol are arteriosclerosis, hypertension and nephritis. The calcium serum levels ought not to be permitted to go above 15 mgm. per 100 cc. No one has yet reported serious or irreversible damage resulting from large doses of vitamin $D_2$, the authors state.

CANNON, P. R.: *Dietary protein and antimicrobic defense.* (Nutr. Rev., June 1949, Vol. 7, No. 6, 161-164).

The author takes exception to a statement which had appeared in Nutrition Reviews, 6, 234, 1948, to the effect that dietary protein represents a minor contribution rather than a major determinant conditioning response to infectious agents. Certainly, he shows, that if dietary protein is not a major determinant in promoting antibody response, then someone should answer the question, what *is* a major factor? It is generally considered that dietary protein is important whenever severe protein deficiency has depleted the tissue protein stores and thereby impaired the body's capacity to activate the mechanisms of both natural and acquired immunity. In the human being this impairment becomes critical only as the result of a severe and prolonged depletion, usually in the range of total protein concentration below 5.9 per 100 ml. of plasma. Such a depletion may be encountered in patients with cancer of the digestive tract, in leukemia, nephrosis and hepatic cirrhosis. Some of the experiments made by various authors have been carried out on patients or animals in whom the protein depletion was really not great. The degree of hypoproteinemia indicates the over-all state of protein depletion, in conformity with the concept of the dynamic equilibrium. The more severe the degree of hypoproteinemia, the more difficult it must become for antibodies to be formed steadily from depleted tissues. Natural resistance, even if it could be shown to be a genic function independent of antibody response, is insignificant as compared with acquired immunity as witness the miraculous effect on smallpox, from Jenner's

work. The author does not feel that a case has been made out against the importance of dietary protein in combatting infections under conditions of protein deficiency.

ZSCHEILE, F. P.: *Role of genetics in food quality improvement.* (Nutrition Reviews, 8, 3, 65-69).

While there are exceptions to the rule, it is generally true that the production of a given nutrient by a plant depends more upon the plant's genetic qualities than upon the type of soil. For that reason, increased production of nutrients, e. g. ascorbic acid, by a tomato plant, may be expected by crossing varieties which contain larger amounts of this substance. Considerable progress already has been made along such lines in various plants, and with respect to their content of various nutrients such as vitamin C, carotene, thiamine, riboflavine, niacine, and essential amino acids. For example, it would be possible to produce a corn hybrid with niacin concentrations of 50 micrograms per gram,—something which would tend to diminish pellagra among corn-consuming human populations. The same may be accomplished in hybrid corn for the essential amino acids. Already a tobacco hybrid has been produced containing only 5 percent the usual amount of nicotine, but otherwise normal. The reduction of coumerin in sweet clover already has been accomplished. Much more may be expected in this genetic field in the future. It appears that the enzyme systems involved in the manufacture of specific nutrients in plants are tied in with, and controlled by the genes themselves.

HOWES, H. A.: *Gastrointestinal allergy.* (Harper Hosp. Bull., 8, 2, 38-40).

Persons exhibiting gastrointestinal allergy usually present also some other form of allergy, particularly allergic rhinitis. Gas, belching, fullness, sometimes nausea and vomiting, and cramps and frequent soft stools are the usual symptoms. A direct relationship must be established between the offending food and the attack and the best way to do this, generally speaking, is to employ an elimination diet, then try pushing the suspected allergen. The most common allergens in food sensitivity are milk, wheat, eggs, orange, corn, fish and beef. The best form of treatment is the complete elimination of the causative food long enough for some tolerance to develop, at which time the patient learns exactly how much of the food he can consume with safety.

HALL, B. E., BETHELL, F. H., MORGAN, E.H., CAMPBELL, D. C., SWENDSEID, WM. E., MILLER, S., AND CINTRON-RIVERA, A. A.: *Observations on the presence of intrinsic factor in extracts of hog stomach and duodenum.* (Proc. Staff. Meet. Mayo Clin., 25, 5, 105-113).

The authors found that concentrated extracts of hog stomach or hog duodenum contained intrinsic factor needed for potentiating vitamin $B_{12}$ in the treatment of pernicious anemia by mouth. The clinical experiments, utilizing pernicious anemia patients in relapse, or those previously untreated by liver, suggest that vitamin $B_{12}$ and intrinsic factor may unite to form a complex possessing greater heat stability than that of intrinsic factor alone. More intrinsic factor was present in the soluble portion of hog's duodenal mucosa than in the insoluble portion. Previous studies had supported the concept of the enzymic nature of the intrinsic factor.

FALOON, W. W., ECKHARDT, R. D., MURPHY, T. L., COOPER, A. M., DAVIDSON, C. S.: *An Evaluation of Human Serum Albumin in the Treatment of Cirrhosis of the Liver.* Journ. of Clin. Investig., July 1949, Vol. 28, No. 4., pg. 583-594.

The recent development of normal human serum albumin for intravenous administration has led to its use in treating clinical states marked by hypoalbuminemia, including chronic liver disease. Previous work with this therapeutic agent has been confined to relatively short-term studies. The present study was undertaken to determine the effect of salt-poor human serum albumin on ascites and edema in chronic liver disease when administered in sufficient amounts to raise the serum albumin concentration and maintain it at or near normal over long periods of time. The results of such therapy attempted in 29 patients with cirrhosis of the liver are presented in this communication. The authors arrived at the following conclusion. Concentrated salt-poor human serum albumin, under the conditions of this study, is neither specific for the relief of ascites nor markedly beneficial in the treatment of the underlying liver disease. In view of the variety of results obtained with concentrated human serum albumin in patients with cirrhosis of the liver, it is concluded that other factors in addition to a reduced serum osmotic pressure, as represented by decreased serum albumin concentrations, are active in the retention of fluid.

FALOON, W. W., ECKHARDT, R. D., COOPER, A. M., DAVIDSON, C. S.: *The Effect of Human Serum Albumin, Mercurial Diuretics and a Low Sodium Diet on Sodium Excretion in Patients with Cirrhosis of the Liver.* Journ. of Clin. Invest., July 1949, Vol. 28, No. 4., pg. 595-602.

The relative importance of serum albumin concentration, portal hypertension and antidiuretic substances in the formation of ascites and edema in patients with cirrhosis of the liver has not been clarified. There is evidence, however, that each of these factors is important.

In an effort to eliminate the factor of hypoalbuminemia, salt-poor concentrated human serum albumin has been given intravenously. Although the serum albumin concentration may by this means be raised to normal, the edema and ascites have not been consistently relieved. Moreover, improvement in ascites and edema is observed in some instances with mercurial diuretics or simply by furnishing a nutritious diet alone.

In an attempt to find an abnormality common to these patients and consistently altered by the apparently unrelated therapeutic agents, the studies of sodium excretion and balance reported here were undertaken.

The patients with cirrhosis of the liver with ascites reported in this communication excreted only small quantities of sodium in the urine regardless of either the quantity of salt administered, or the route of its administration. The failure to excrete sodium in amounts adequate to achieve sodium equilibrium occurred in spite of the maintenance of normal serum albumin concentration by repeated injections of concentrated salt-poor human serum albumin.

The urinary excretion of sodium was usually increased by the administration of mercurial diuretics or of salt-poor human serum albumin and also during a spontaneous decrease in ascites and edema formation.

A low sodium but otherwise adequate diet decreased the rate of ascites formation, while larger quantities of administered sodium led to a proportionately increased rate of formation.

Although several factors might have led to the failure of these patients to excrete sodium, there was no evidence that any one was solely implicated.

The relative importance of the failure to excrete sodium, of hypoalbuminemia and of portal hypertension in the genesis of ascites could not be precisely defined.

ECKHARDT, R. D., FALOON, W. W., DAVIDSON, C. S.: *Improvement of Active Liver Cirrhosis in Patients Maintained with Amino Acids Intravenously as the Source of Protein and Lipotropic Substances.* Journ. of Clin. Invest., July 1949, Vol. 28, No. 4., pg. 603-614.

Because of the frequent digestive disturbances encountered in patients with liver cirrhosis, occasions arise when an adequate intake of nutritious foods cannot be maintained, and supplemental or complete intravenous feeding would appear indicated. The desirability of administering protein hydrolysates intravenously to patients with hepatic insufficiency has been the subject of controversy. Thus, it has been stated that amino acids administered parenterally to such patients are not as promptly deaminized and result in a higher incidence of autoward reactions than when administered to normals. Since other investigators were of an opposite opinion, the experiments reported here were undertaken to clarify the controversy. Observations were made of the clinical tolerance, the metabolism and excretion and the therapeutic value of a ten percent solution of amino acids administered intravenously in amounts of 500-1000 cc. daily for from two to four weeks as the sole source of nitrogen and of lipotropic substances to four patients with active cirrhosis of the liver.

The results indicate that intravenously administered amino

acids are well tolerated by patients with severe liver disease, are metabolized and excreted in a manner differing little from normal and may promote clinical improvement when administered as the sole source of nitrogen and of lipotropic substances.

Walter Cane.

McCLURE, F. J.: *Fluorine in foods.* (Pub. Health Reports, Aug. 16, 1949, 64, 34, 1061-1074).

A study of recent analytical data for fluorine in foods indicates that the majority of foods found in the average diet contain from 0.2-0.3 parts per million or less fluorine in the food as consumed. Tea and seafoods are notable exceptions the former upwards of 75 to 100 ppm. fluorine in the dry tea, while seafoods may contain 5 to 15 ppm. fluorine. Cow's milk contains about 0.1-0.2 ppm. fluorine. Fluorine added to the cow's ration or drinking water has no influence on the milk-fluoride. Fluorine in soil and water has little or no influence on the fluorine content of edible plant produce. It appears that natural food-borne fluorine is largely available for body assimilation. Exclusive of drinking water, the average diet appears to provide 0.2-0.3 mg. of fluorine daily. However, it has been observed that an additional intake of fluorine during formative tooth life, via drinking water containing 1.00 ppm. or slightly more fluorine, is a distinct dental health advantage. It is justifiable to consider the possibility of a direct dietary fluorine supplement where drinking water does not provide a dental optimum quantity of fluorine.

PREJEAN, O. V. AND GRIFFIN, J. B.: *Diabetes mellitus and pregnancy.* (Texas State J. M., Sept. '49, 45, 9, 627-630).

Pregnancy and untreated diabetes are basically incompatible. Rigid control of the disease is needed for successful reproduction. During the pre-natal period, close observation must be made for insulin reactions, toxemia, hydramnios and fetal death. Termination of pregnancy at the 37th week of gestation seems to give best results. A pregnant diabetic usually can be carried to a stage of fetal viability. Therapeutic abortion is contraindicated.

# EDITORIALS

## PEPTIC ULCER AND "ORDINARY" ANXIETY

Franz Alexander made a deep impression on gastroenterology when he propounded his theory of the causation of peptic ulcer in 1934. The infantile desire to be loved is equated by the infantile ego with security and is symbolized by being fed. Later, should the adult ego, through frustration, reject the normal satisfactions of adult life, a regression occurs of such a nature that in his desire for dependency, the individual unconsciously falls back upon the infantile pattern, incidentally setting up a continuous gastric secretion and hypermotility *as if he were being fed*. This overstimulation of the digestive apparatus quickly predisposes, through injury to the gastric or duodenal mucosa, to the formation of peptic ulcer. There can no longer be much doubt that anxiety of various types is capable of producing the degree of digestive stimulation needed for the formation of ulcer. Wolf, Wolff and Mittelman, particularly by their direct observation of the gastric mucosa in their fistulous subject, "Tom," have made it clear that the stomach lining is an organ highly reactive to various emotional states, and that the hypersecretion induced is capable, in the presence of minor injury to the gastric mucosal cells, of initiating the evolution of a peptic ulcer.

The question arises, however, as to whether or not a regressive tendency is required. In other words, can an ulcer evolve in a person who is perfectly mature from an emotional standpoint? Sullivan and McKell (1), after studying 1000 cases of peptic ulcer in New Orleans, believe that while Alexander was correct in his description of the emotional cause of ulcer, he was incorrect in assuming that all cases occur in persons as a result of a personality regression. In only a small fraction of their cases did they note a definite neurotic background. The causal anxiety, in the majority, was produced by minor stresses in the life-situation. There was a third group in whom the actual stress was of a decidedly severe nature, but in neither of these two groups was there evidence of regressive tendencies. Sullivan and McKell could find no evidence that a single case of peptic ulcer had ever been psychoanalyzed, yet Alexander himself psychoanalyzed at least one such case and obtained healing of the ulcer through psychotherapeutic interviews. Perhaps, in spite of the difficulties of psychoanalyzing ulcer patients, it should be done and final conclusions reserved. Many physicians with ulcers of their own would like to believe that "ordinary" anxiety is a sufficient cause.

(1) Sullivan, A. J. and McKell, T. E.: Personality in peptic ulcer. C. C. Thomas, Springfield, 1950.

## OUR ATTACK ON GASTRIC CANCER

Until some fool-proof method of making an early diagnosis of carcinoma of the stomach is discovered, the mortality from this disease must continue to remain high. Patients, because of the nature of the condition, seldom present themselves to their physicians early in its course, and even when they do, a diagnosis usually is *not* made. The failure to make an early diagnosis rests upon the usually vague character of the complaint, and quite frequently upon negative roentgenological findings. Even gastroscopy, when it is used, is by no means an infallible method. Microscopic examination of the stained smear of centrifuged gastric contents is still in its infancy, and the recognition of malignant cells requires extensive practice. The net result of these uncertainties is that a high proportion of early carcinomas is overlooked.

As recently emphasized by Edwards (1) the history is by far the most significant element in the entire examination. A person of middle age presenting digestive symptoms for *the first time*, or presenting an unexplained anemia, ought to be suspected of gastric cancer even though all other investigations have yielded negative or equivocal results. Furthermore, it is important that internists develop the courage to refer such patients for immediate laparotomy. Only in this way is there any present hope of cutting down the appalling mortality. A general feeling of lassitude, some weight loss and perhaps ulcer-like symptoms ought to increase the physician's suspicion of cancer.

(1) Edwards, H. C.: Carcinoma of the stomach, B.M.J., April 29, 1950, 973-978.

Roentgenologists usually realize the danger in returning a negative report in the case of a patient having these vague yet suggestive symptoms, but, of course, they cannot send any other report where no lesion is found. The responsibility, in instances of negative x-ray reports, rests squarely on the shoulder of the attending physician. Until we realize that sudden dyspepsia and asthenia in middle life is likely to prove a surgical disease, we are not doing our full duty to the patient.

# BOOK REVIEWS

PERSONALITY IN PEPTIC ULCER. A. J. Sullivan, M.D. and T. E. McKeil, M.D., 100 pages. Charles C. Thomas, Springfield, Ill., 1950, $3.00.

The authors, in assessing the diverse personality factors in peptic ulcer, emphasize that the psychosomatic aspects of the disease were not adequately recognized until within the past decade. They examine Alexander's hypothesis of ulcer causation viz., the persistence of an infantile dependency requiring food for gratification, but raise the objection that Alexander's ideas were based on the study of only nine cases, six of duodenal ulcer of whom only three were active, and three cases of gastric neurosis. They found Alexander's theory applicable to only 11 percent of their last 200 cases. However, Alexander's contention that chronic excitation of the stomach by emotional tension is the mechanism of ulcer production is regarded by the authors as correct. But conflicts such as anxiety especially, do not need to be on the dependency basis, but may arise from the life situation in a mature person. The authors deal with the theory of multiple etiology and then proceed to examine the ulcer personality, and emphasize the restless drive, the versatility, the emotional responsiveness, self-reliance, willingness to assume responsibility, good sexual adjustment, and the overpowering urge for success and true superiority. Recurrences usually are precipitated by minor crises related to occupation, but in some cases a deeper emotional conflict is involved. In still others, the anxiety is produced by some unusual and crushing conspiracy of circumstance. Such a "personality profile" as the authors present is not too different from Dunbar's profile of coronary occlusion. The book has the virtue of brevity, but in a short discourse the authors seem to have considerably clarified the question of the nature of "peptic ulcer people." They have largely removed the disease from the realm of emotional immaturity.

THE BRITISH ENCYCLOPEDIA OF MEDICAL PRACTICE: MEDICAL PROGRESS 1950. Edited by Lord Horder. Butterworth and Co. Ltd., London, England, 1950.

There are 163 pages devoted to short resumes by appropriate authorities particularly dealing with subjects of keenest interest during the past 12 months—the newer treatment of the rheumatic disorders, geriatrics, B.C.G. vaccination, streptomycin in pulmonary T.B., vagotomy for ulcer, sympathectomy in hypertension, chemotherapy of cancer, vaginal smear diagnosis, Hirschsprung's disease, absorption of vitamin A, streptomycin in infantile gastroenteritis, as well as many other topics. Under gastro-enterology, F. Avery Jones emphasizes the high incidence of gastric cancer in pernicious anemia (9.3 percent). Chronic relapsing pancreatitis, recently described by Mayo Clinic authors, is reviewed. There are sections on bacteriology, endocrinology, infectious diseases, neurology, tropical medicine, venereal diseases, anesthesia, public health and pharmacology. 360 pages are devoted to exhaustive abstracts.

THE MERCK MANUAL. 1592 pages. Published by Merck & Co. Inc., Rahway, N. J., Reg. Ed. $4.50, Thumb-Index Ed. $5.00.

The Merck Manual, now in its 8th edition, has become even more popular than ever. T. E. Jennings, Manager, Public Relations Dept. of Merck and Co. states that the first printing of 75,000 copies was required to fill advance orders. The book covers the entire field of medical practice, is up-to-date and is one of the few inclusive *vade mecums* available to the profession. The value of the work may best be described by saying that if any physician knew all that it contains, he would be an expert practitioner. It is ably written and it is too bad that the Editor's and various authors' names are not revealed. It is printed on Bible paper. Certainly the price asked is not excessive for so large a book.

# GENERAL ABSTRACTS OF CURRENT LITERATURE

ISRAELS, M. C. G. and WILKINSON, J.: *Risk of neurological complications in pernicious anemia treated with folic acid.* Brit. Med. J. Nov. 12, 1949, 1072-1075.

During a 3 year period, out of 20 patients with pernicious anemia thirteen, who at the first had had no neurological involvement, developed cord changes while being treated solely with folic acid. Three cases with initial neurological symptoms and signs became worse neurologically after the same therapy. The blood levels were quite unrelated to the development of the cord changes. Four patients are quite well after 2 or 3 years on doses of from 5 to 20 mg. folic acid daily, given orally. These results indicate that folic acid is not a safe remedy in pernicious anemia and certainly ought not to be used in the presence of cord changes. All the patients who had slipped responded well, once the treatment had been changed to liver extract. It would appear that folic acid, while effective in inducing and maintaining blood remissions in this disease, is not only ineffective but possibly it is positively harmful with respect to neurological degenerations. Obviously there is some as yet unexplained dissociation between the cord and bone marrow aspects of pernicious anemia.

DOUGRAY, T: *Antihistamines in the treatment of nausea and vomiting of pregnancy.* Brit. Med. J. Nov. 12, 1949 1081-1083.

78 per cent of pregnant women complaining of nausea and/or vomiting were cured of the symptoms by the persistent use of an antihistaminic. The drug used was phenergan, of which one 0.025 gm. tablet three times daily usually proved effective. Drowsiness, when it occurred, was overcome by giving 5 mg. of amphetamine sulfate. The total number of patients thus treated was 94.

NEEFF, J. R.: *Viral hepatitis; problems and progress.* Ann. Int. Med. 1949, 31, 5, 857-870.

While this article deals with viruses III and SII and several problems connected with viral hepatitis, the practical point in prevention is the author's emphasis upon the necessity of using individually sterilized syringes and needles for each patient. He thinks boiling for 5 minutes kills the viruses provided all adhering dried serum is first removed by thorough cleansing.

AMER. JOUR. DIG. DIS.

Martyn, G: *The relation of staphylococcus pyogenes to infantile diarrhea and vomiting.* Brit. Med. J. Nov. 1949. 1146-1148.

A bacteriological examination of the stools in 119 cases of infantile diarrhea and vomiting showed the presence of Staph. pyogenes in 44.5 per cent, but the organism was found in 46 per cent of the controls. The conclusion appeared mandatory that the organism bears no causal relationship to the disease.

Hird, A. J: *Mikulicz's syndrome.* Brit. Med. J. Aug. 20, 1949. 416-418.

Mikulicz's syndrome (or disease) is rare. A case occurring in a 73-year-old man is described, in which death resulted after 14 months. He had the characteristic enlargement of the salivary and lachrymal glands, splenic enlargement and a sternal puncture that showed that 90 to 95 per cent of the nucleated cells were lymphocytes. The peripheral blood showed an absolute lymphocytosis but a rather low total white count, about 6000. Following x-ray therapy of the enlarged glands and the skin areas in general, he obtained one good remission, although the sternal marrow picture and the enlarged spleen did not change. Probably Mikulicz's syndrome is a manifestation of a general involvement of the lymphoid tissues rather than a local disease of the lachrymal and salivary glands.

Sheedy, J. A.: *Intestinal parasites in patients with viral hepatitis.* Bull. U. S. Army Med. Dept. 1949. IX, 12, 998-1004.

96 patients having proved viral hepatitis were surveyed for intestinal parasites. All were serving in the European theater. It was thought that if the viral disease represented poor sanitation perhaps parasitic contaminations might also be present. This was found not to be the case. Parasites were found in about 52 per cent of the series. Amebiasis was present in about 6 per cent. The incidence of other parasites showed no marked difference from that reported by other investigators for the U. S. as a whole.

Voegtlin, W. L., Broz, W. R. Tupper, W. E. and Robinson, M. W.: *Liver function in chronic alcoholic patients. II Correlation between elements of the history and presence of liver dysfunction as indicated by laboratory tests.* Gastroenterology, November 1949, 13, 5, 391-400.

It was not found possible to predict hepatic dysfunction from the history of chronic alcoholics. The syndrome of alcoholism does not predispose to the development of any progressive degenerative liver disease such as portal cirrhosis. Liver dysfunction, as seen in alcoholism, is reversible on cessation of the drug.

Wolf, S. and Almy, T. P: *Experimental observations on cardiospasm in man.* Gastroenterology, Nov. 1949, 13, 5, 401-402.

The authors infer that cardiospasm may occur as a part of a biological reaction to stress and, in its early stages, is functional and reversible. Normal persons occasionally reacted with cardiospasm to threats and stress, and cardiospasm may be induced by the local application of heat, cold, or chemical irritation to the esophagus. The esophageal obstruction of cardiospasm was often found to be associated with marked hypermotility of the lower 2/3 of the esophagus.

Alvarez, Walter C: *A simple explanation for cardiospasm and Hirschsprung's disease.* Gastroenterology, Nov. 1949. 13, 5, 422-429.

Alvarez suggests that since smooth muscle contracts down to a knot when separated from its nearest ganglion cell, the simplest explanation for cardiospasm and the blockage at the distal end of megacolon is the loss of the ganglion cells in Auerbach's plexus. Such loss might be due to toxic insults such as diphtheria or tetanus, with their high neurotoxic elements, or to such a disease as a subclinical and unrecognized anterior poliomyelitis. An actual absence of the cells of Auerbach's plexus has been confirmed by pathologists who critically examined this point in cardiospasm. Alvarez plays down the importance of emotional influences in producing cardiospasm while admitting that they exist to some extent.

El-Gholmi, A. A., Hanna, M., El-Kholy, S. E. D. and El-Sokky, Z: *A new sulfonamide in the treatment of infantile dyspepsia.* Arch. Pediat. Nov. 1949, 66, 11, 492-499.

The authors report good results in treating gastrointestinal infections in infants by the use of Formo-Cibazol. This compound, introduced by Ciba, Ltd., Basel, Switzerland, is a condensation product of 2 molecules of sulfathiazol and 3 molecules of formaldehyde. Streptococcus fecalis was the organism most commonly found in the stools. The drug can safely be given in doses up to 0.3 gms. per kilo of body weight per day, given in divided doses every 4 to 6 hours.

Rang, H. O. Bechgaard, P. and Nielson, A. L.: *Low salt diet in treatment of hypertension and hypertensive heart disease.* Brit. Med. J. Nov. 1949, 1203-06.

26 patients with hypertension, in some associated with cardiac failure and/or kidney disease, were treated with a diet containing less than 1 gm. sodium chloride per diem. Sixteen of these showed a considerable reduction in both systolic and diastolic pressures, which rose to some extent again after the daily addition of 4.5 gms. of salt. The low salt diet was effective in clearing cardiac edema. The treatment is contraindicated in some cases of chronic nephritis. In 6 cases abnormal T waves in the ekg improved.

De Silva, P. C. C.: *Amebiasis in infancy.* Brit. Med. J. Nov. 1949, 1208-10.

From a study of the stools of infants in Colombo the author found, contrary to accepted opinion, that amebic dysentery was as common in infants as in adults. Up to 2 years of age, 15.9 per cent of 291 cases were found to be due to amebiasis. Response to treatment by emetine parenterally and carbosonne orally was satisfactory in 80 per cent of the cases followed up.

Nardell, S. G.: *Acute phlegmonous cecitis.* Brit. Med. J., Nov. 1949, 1210-11.

Acute phlegmonous cecitis is rare and is difficult to differentiate clinically from acute appendicitis. The presence of a well-defined very tender mass in an apparently early case of acute appendicitis might give rise to the suspicion of acute phlegmonous cecitis. To remove the appendix does no harm. Both of the author's two cases resolved rapidly through the use of penicillin and sulfamerazine. Surgical attack on the cecum should be avoided.

Reynolds, L., Corrigan, K. E. and Hayden, H. S.: *Early detection of cretinism and other diagnostic uses of radioactive tracers in infancy and childhood.* Harper Hosp. Bull. 8, 1, 4-6.

By the use of orally administered radioactive iodine ($I^{131}$) to infants and children in doses which, in babies, does not exceed 5 millicuries, and is therefore harmless, it is possible to recognize cretinism and extremely severe cases of hypothyroidism at a very early age and so institute thyroid therapy at once, with excellent eventual results. The diagnosis is made by detecting the amount of tracer iodine which is taken up by the thyroid gland, and also by the detection of the amount which is excreted in the urine. Similarly, radioactive phosphorus ($P^{32}$) has been employed for the early detection of malignancy such as osteogenic sarcoma.

Fisher, J. H.: *Duodenal ulcers in infants.* Am. J. Dis. Child. Jan. 1950, 79, 1, 50-58.

Fisher describes duodenal ulcer in 4 infants, the oldest being 8 months. Antemortem diagnosis was not made. All presented feeding difficulties, anemia, vomiting, diarrhea and marasmus. Blood was present in the stools in two cases. It is suggested that peptic ulcer should more frequently be considered as a possible cause of such syndromes in infants.

Veghelyi, P. V., Remeny, T. and Sos, J.: *Cystic change in the pancreas.* Am. J. Dis. Child. Jan. 1950, 79, 1, 65-68.

The Budapest workers produced cystic changes in the pancreas of rats by the subcutaneous injection of carbon tetrachloride. No bronchial changes occurred in the rats and

the pancreatic lesions produced were somewhat different from the lesions of cystic fibrosis in children.

LOWE, C. U., MAY, C. D., STAUFFER, H. M. and NEUHAUSEN, E. D. B.: *Fibrosis of the pancreas (Enterogastrone and the 'duodenal mechanism' in relation to increased appetite.)* A. J. Dis. Chil. Jan. 1950, 79, 1, 91-98.

Normally a fat meal delays gastric emptying time but it fails to do so in cases of pancreatic fibrosis, unless the patient has been given pancreatin prior to the barium meal.

The 'deficiency pattern' in the small bowel is probably due to the activity of enterogastrone. Such a pattern was not noted in children with fibrosis of the pancreas unless pancreatin was administered to them prior to the examination.

It was thus suggested that both the 'duodenal mechanism' and the 'deficiency pattern' depend upon the stimulation or formation of enterogastrone, which may in turn depend primarily upon the pancreatic secretion. The voracious appetite in pancreatic fibrosis is controlled by giving pancreatic extract.

PALMER, EDDY D.: *Tuberculosis of the stomach in tuberculosis.* Amer. Rev. Tuberculosis, Jan. 1950, 61, 1, 116-128.

Tuberculosis of the stomach, though rare, presents ulcerous, infiltrative, tumorous and inflammatory types. The antrum and the lesser curvature of the pars media most frequently are affected. Pre-operative gastroscopic diagnosis is possible in some cases. Ulcers with undermined edges and serpiginous outlines and with nearby superficial tubercles are characteristic.

The stomach of the tuberculous patient who has no gastric tuberculosis shows depressed secretory activity and frequently a chronic atrophic gastritis presumably due to nutritional deficiency.

ROBBINS, E. D.: *Hypometabolism or hypothyroidism?* Mississippi Valley Med. J. Jan. 1950, 72, 1, 9-15.

Robbins reviews the difficult subject of lowered metabolism not caused by hypothyroidism. Where the thyroid is not involved, the plasma lipoids are of normal values. The amount of protein-bound iodine in the blood is probably a better indicator of thyroid function than the metabolic basal rate. A person from whom the thyroid has been completely removed requires only ¼ to ½ grain of thyroid extract daily to prevent myxedema, yet hypometabolic patients sometimes can tolerate from 3 to 7 grains of thyroid per day. The group showing "non-myxedematous hypometabolism" includes many normal persons, while the rest display a number of morbid states among which thyroid insufficiency plays a small and even questionable role.

POPP, W. C., BARGEN, J. A. and DIXON, C. F.: *Regional enteritis; roentgen therapy.* Staff Meet. Mayo Clin. Jan. 4, 1950, 25, 1, 1-5.

Preliminary reports on the use of x-ray treatment in regional enteritis in 59 cases indicate that very favorable results were obtained in half the cases, and a quarter the balance improved. Roentgen therapy seldom alters the radiographic appearance of the affected gut. The fibrosing type of case is more amenable to treatment than the ulcerating type. X-ray treatment appears to increase fibrosis. It is hoped by combining roentgen with surgical and medical forms of treatment that better general results will be obtained.

MUSGROVE, J. E.: *Elevated serum amylase levels associated with perforated gastroduodenal lesions.* Staff Meet. Mayo Clin. 25, 1, 8-10.

In 3 acute abdominal emergencies, each of which had shown prior to operation or autopsy, from 50 per cent to 100 per cent increase in serum amylase, Musgrove found no pancreatic lesion, but in each case a perforated viscus. In two of the cases a duodenal ulcer had perforated and in the other a sarcoma of the stomach had perforated. It is evident from these findings that perforation of the stomach or duodenum can produce an elevation of serum amylase without pancreatic disease. Obviously the pancreatic juice is poured through the perforation opening into the peritoneal cavity and absorbed therefrom. Other lesions capable of elevating the serum amylase are acute inflammation of the salivary glands, involvement of the pancreas by adjacent pathological processes and renal failure, in the last instance due to depressed excretion of amylase. In cases in which the serum amylase is elevated as much as 500 per cent above normal, we are almost certainly dealing with acute pancreatitis.

ROGERS, K. B., KOEGLER, S. J. and GERRARD, J.: *Chloramphenicol (chloromycetin) in treatment of infantile gastro-enteritis.* Brit. Med. J. Dec. 31, 1949, 1501-1504.

In Birmingham, Bact. coli B.G.T. has been found associated with epidemic infantile gastro-enteritis. The disease failed to respond to sulfonamides, penicillin or streptomycin but there has been a "most encouraging" response both clinically and bacteriologically to chloromycetin. The infants received 75 mg. per pound of baby weight per day in 6 or 8 divided doses.

GRAUSMAN, ROLAND I. and ROGERS, SEYMOUR S.: *Surgery of ileal tumors.* Report of a case of intussusception led by lipoma of ileum, Am. J. Surg. 77, 3, 387, March 1949.

The terminal ileum is the most common site of tumors of the small intestine. Most of these tumors are benign and their clinical importance depends upon the complications of obstruction, necrosis or intussusception. These tumors are diagnosed by symptoms of vague, colicky, intermittent, pain in the right lower abdominal quadrant. The pain increases in intensity with the onset of the aforementioned complications. Roentgenograms and particularly fluoroscopy are useful aids in diagnosis. The suggestive radiographic signs are filling defects, deformity of bowel outline and evidence of distended bowel. The treatment is surgical and consists of enterostomy and exclusion, reduction of an intussusception and enterostomy; or resection of the tumor-bearing area.

A case of irreducible, ileocolic intussusception caused by a lipoma of the ileum and treated by resection of the affected bowel and an ileotransversostomy, is described.

Franz J. Lust.

LADIN, PHILIP: *Torsion of the appendices epiploicae.* N. Y. State J. Med. 49, 18, 2168, Sept. 15, 1949.

The torsion of an appendix epiploica as a cause of acute abdominal signs and symptoms is not usually considered. In asmuch as five cases were found in the records of a small hospital, this condition may be more common and should be looked for more often. In a patient who presents a long history (two or more days) and whose physical findings are relatively mild this condition should be suspected. If the clinical condition warrants surgical intervention, it should be looked for at operation. Removal of the appendix epiploica should be done with careful dissection of the base. The literature was reviewed briefly, and five cases were reported in this paper bringing the total number of reported cases up to 73.

Franz J. Lust.

HEIKEL, P. E.: *Roentgenologic observations on medication with pilocarpine in hypertrophic pyloric stenosis.* Ann. Med. Intern. Fenniae 36, 3, 482, 1947.

In 18 cases of clinically manifest hypertrophic pyloric stenosis the effect of 2 mg of pilocarpinum hydrochloricum per os after a barium meal in the stomach has been roentgenologically observed. Peristalsis increased in 17 cases, grew weaker in one case. Stenosis in the canalis egestorius was dilated in 12 cases, remained unchanged in 6 cases, in no cases remained constricted. The evacuation of the stomach began earlier in six cases where it had previously been delayed, and remained normal in all other cases. The amount of barium evacuated into the intestine after 1½ hours increased in 14 cases, remained unchanged in two, and decreased in two. In agreement with the results of earlier examinations the dilatation of the stenosis appears to take place in the muscularis mucosae, not in the hypertrophic muscularis propriae.

Franz J. Lust.

## PHYSICIAN PRISONERS

To obviate the recurrence of certain hardships and limitations suffered in previous wars by physicians of the Armed Services who fell into enemy hands, The World Medical Association recently reported that it is laying plans to have all nations fix a status for the captured doctor which, while entitling him to the formal rights of a prisoner of war, will not actually designate him as one.

This announcement was made by Dr. Louis H. Bauer, Secretary General of the Association at its world headquarters in the New York Academy of Medicine, 103rd Street and Fifth Avenue. At the same time Dr. Bauer reported that during the last several months interest in the Association had increased so sharply that its United States Committee, from which the organization derives most of its financial support, has established a public information service at 444 Madison Avenue under the direction of Noyes & Sproul, Inc., of that address.

The Secretary General of the Association will be one of five Americans attending the annual meeting of the organization's Council April 24-28 in Copenhagen, Denmark where the doctor-war prisoner issue is expected to be discussed. Although not himself a member of the Council (the Association's administrative unit of thirteen members), Dr. Bauer will be accompanied to Copenhagen by two physicians who will officially represent the United States in that body. They are The World Medical Association's President-Elect, Dr. E. L. Henderson of Louisville, who is also President-Elect of the American Medical Association and Dr. R. L. Sensenich of South Bend, Ind., the immediate Past-President of the A. M. A., Dr. Morris Fishbein, Editor of The World Medical Association Bulletin, and Dr. Bauer's Executive Assistant, Miss Margaret L. Natwick, will also attend the meeting.

In discussing the status to be sought for the enemy-interned physician, Dr. Bauer pointed out that his organization will base its position on resolutions made in Stockholm, Sweden, last August by the International Committee of Military Medicine and Pharmacy. These stipulated that "the intangible principle of non captivity of the sanitary staff has to be fixed as an elementary basis . . . for the protection of wounded people and prisoners." Emphasizing that "in no case should its (that is, the sanitary staff's) members be treated as prisoners of war" these Stockholm resolutions said that the staff's extended immunity "should be recognized not as a personal privilege, but as a functional and social necessity in the interest of mankind." The final outcome of the deliberations in Stockholm was the following recommendation:

"Retained personnel shall not be deemed to be prisoners of war, but shall enjoy all the rights of the latter." Furthermore, there has been added: "Belligerents shall see to it that this personnel receives the same allowances and the same pay as does the corresponding personnel in their army."

While seeking thus to liberalize the status of doctors seized by the enemy, The World Medical Association would yet have them enjoy those few special rights which, by international agreement, have been doled out to officially designated prisoners of war in the past. Dr. Bauer cited Red Cross gift packages as constituting one such privilege. "These packages, alone," he said, "have revived morale, and, on occasion, have even saved the lives of numerous prisoners on enemy starvation diets in the past. Certainly an interned doctor, whether formally defined as a prisoner of war or not, should be entitled to his share of such Red Cross help at least." While in the past he has sometimes had these privileges, nevertheless his status has not been clearly enough defined to guarantee it.

Efforts also will be made at the Copenhagen meeting to solve a problem in anesthesia which, according to Dr. Bauer, "will have a direct bearing on many of the world's 500,000-odd medical practitioners." This involves international standardization, wherever possible, of gas cylinders and other anesthesia equipment as to color, size, and other details and thus minimize the chances of costly—sometimes even fatal—mistakes in the operating room. Other matters to be discussed at the forthcoming Council meeting are international nomenclature; medical security; medical education; the medical press, and industrial medicine.

Pointing out that the progressively expanding World Medical Association—culmination of an idea advanced twenty-five years ago and actually organized in 1947—embraces in its membership the official medical societies of forty nations, Dr. Bauer cautioned against confusing his group with the World Health Organization. Although complementing each other the two units derive their support from entirely different sources and are wholly distinct in their nature and purpose. The World Medical Association, Dr. Bauer explained, represents the doctors and the national medical association of the world. It concerns itself primarily with medical care and promotes high standards of medical education and practice on a global basis, effects a better liaison among the doctors of the world, and promotes the betterment of international relations. The Association is supported entirely from voluntary contributions and it has only professional memberships.

The World Health Organization, on the other hand, is a subsidiary of the United Nations and, as such, represents the governments of the world. It is chiefly interested in Public Health and its membership is non-medical as well as medical. This organization is financed exclusively by governmental appropriations.

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## LIAISON

The "happy liaison" between the medical profession and America's ethical drug industry was emphasized May 13 and May 14 by E. Claiborne Robins, president of the A. H. Robins Co. of Richmond, Va., in two broadcasts over "The Voice of America" which altogether reached the English-speaking peoples of forty-five nations.

As the Department of State's major promotional instrument for fostering the democratic spirit abroad, "The Voice" is rebroadcasting Mr. Robins' text in the many languages of the European and Latin American nations which it covers.

Discussing "The Manufacture of Ethical Drugs in the United States of America," Mr. Robins, in part, said:

"In the United States the ethical drug industry subsidizes numerous medical men who invariably serve as consultants for the ethical drug manufacturer. Because of this happy liaison, with its constant interchange of laboratory and clinical findings, the American pharmaceutical industry is now widely regarded by the physi-

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| Calcium Pantothenate | 2.5 milligrams |
| Niacinamide | 20.0 milligrams |

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1. Sollmann, T.: A Manual of Pharmacology. Philadelphia, W. B. Saunders Co. 7th ed., 1948, p. 938.
2. Batterman, R. C., and Ehrenfeld, I.: Gastroenterology, 9:141, Aug., 1947.

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cian as indispensable to his professional progress."

Tracing the step-by-step development of one particular drug product as typical of the many, Mr. Robins told how research work at the Mayo Clinic had inspired the course of its production. He also pointed out that, whether headquartered in the United States or in any other civilized country, all alert manufacturers of ethical drugs depend for guidance on "that free, international exchange of medical research on which their industry is so squarely based."

## RESEARCH FELLOWSHIPS—THE AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1951-June 30, 1952. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work.

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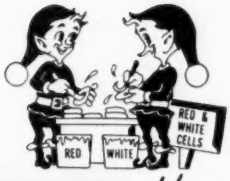


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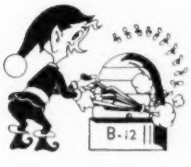


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